Systemic Lupus Erythematosus:

REVIEW OF THE LITERATURE AND CLINICAL ANALYSIS OF 138 CASES

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SYSTEMIC LUPUS ERYTHEMATOSUS: REVIEW OF THE LITERATURE AND CLINICAL ANALYSIS OF 138 CASES*

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TABLE OF CONTENTS

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I. INTRODUCTION

During the past few years there has been widespread interest in those diseases involving connective tissue. Although the etiology of systemic lupus erythematosus (SLE) is still unknown, knowledge of the disease has advanced along several lines. The discovery of the L.E. cell phenomenon has resulted in more accurate diagnosis and opportunity for broader clinical and experimental studies of this disease. Important has been the ability to control many of the distressing clinical manifestations by the administration of adrenocorticotropic hormone (ACTH) and various adrenal steroids, even though the basic evolution of the underlying process may not be altered. In view of these recent developments, it seemed worthwhile to assemble the available information about SLE and to review it in the light of our experience with this disease during the past eight years. The most important goal is discovery of its etiology, but since this information is lacking at present, a thorough review of the natural history of SLE may possibly stimulate new avenues of approach to its study.

In 1949 the clinical course of SLE as observed in 32 patients at the Johns Hopkins Hospital was reviewed (258). Subsequently, an additional 106 patients, proved to have this disease, have been observed. It is the purpose of this presentation to analyze the clinical features as manifested in these 138 patients, and to review the pertinent material previously published concerning this disease.

In each of these 138 patients, the clinical diagnosis of SLE was established either by autopsy examination, the finding of L.E. cells in the peripheral blood or through study of material obtained at operation. Autopsy examinations were performed upon 52 patients. Six individuals underwent splenectomy because of thrombocytopenia and the characteristic changes of lupus were found in the removed organ. L.E. cells were found in the peripheral blood of 79 patients, all of whom had a clinical course compatible with SLE. In the remainder, the diagnosis was confirmed by the finding of characteristic changes of biopsy of skin, muscle or lymph node. Fifty-two of these patients were treated symptomatically, while the remainder received cortisone or ACTH. Sixty-two of those receiving hormone therapy have been followed for varying periods of time.

II. HISTORICAL DEVELOPMENT

A review of the historical development of our knowledge of SLE serves to emphasize the remarkable variability in the clinical picture as evidenced by the number of years which passed before the protean manifestations could be grouped together as parts of a systemic disease. It also illustrates the difficulty of determining the full spectrum of a systemic disease whose course is characterized by exacerbations and remissions until a specific diagnostic test becomes available.

First to attract attention were dermal lesions of lupus erythematosus described under the term "erythema centrifuge" by Biett in 1828 (24). Later Hebra gave a more detailed description and noted two types: disc-like patches and detached or confluent lesions of smaller size (114). In 1851, Cazenave (40) introduced the term lupus erythematodes in order to distinguish this disease

from lupus vulgaris Kaposi designated the two forms described by Hebra as the discoid form and lupus erythematosus disseminatus.

The first description of SLE was that by Kaposi in 1872 (135). He observed patients whose illness was characterized by fever, toxic manifestations, and cutaneous lesions resembling those of erysipelas to which he gave the name "erysipelas perstans faciei" The significance of the systemic manifestations of this disease, and the relationship of the visceral lesions to those in the dermis were first emphasized by Osler (189) He not only described essentially all of the varied clinical manifestations known to occur, but also pointed out instances in which the disease ran its entire course to death without the development of cutaneous manifestations The remarkable fact is that his description of this disease, as illustrated by the following quotation from one of his papers, was made without benefit of pathological studies "By exudative erythema is understood a disease of unknown etiology with polymorphic skin lesions, hyperemia, edema, and hemorrhage-arthritis occasionally, and a variable number of visceral manifestations of which the most important are gastrointestinal crises, endocarditis, pericarditis, acute nephritis and hemorrhage from mucosal surfaces. Recurrence is a special feature of this disease and attacks may come on month after month or even throughout a long period of years The attacks may not be characterized by skin manifestations The visceral symptoms may be present and to the outward view the patient may have no indications whatever of erythema exudativum" In 1904, Jadassohn (126) reviewed the disease and referred to the frequency of involvement of the joints, serous and mucous membranes and kidneys, and of constitutional manifestations such as fever, and prostration

These important contributions of Sir William Osler and of Jadassohn were all but forgotten until the 1920's when interest in SLE was rekindled by a series of papers appearing during that period Goeckerman (80) presented a comprehensive clinical analysis of acute lupus erythematosus in 1923, and leucopenia and thrombocytopenia were added to the diagnostic criteria (136). The initial manifestations were recognized as following a definite pattern requiring differentiation from other general disorders having dermal manifestations In 1924 Libman and Sacks (160) described four cases of non-bacterial endocarditis, two of which had cutaneous lesions of lupus erythematosus. The cardiac alterations were described in detail by Gross (92, 93) in a series of articles appearing between 1932 and 1940

One of the important landmarks was the publication in 1935 by Baehr, Klemperer, and Schifrin (5) of a paper entitled "A Diffuse Disease of the Peripheral Circulation (Usually Associated with Lupus Erythematosus and Endocarditis)". In this paper the clinical and pathological findings in 23 cases were analyzed offering the most complete description of the clinical picture up to that time These authors summarized the clinical course as characterized by irregular fever [illegible] tendency to remissions of variable duration, involvement of synovial and [illegible]

their 23 patients were female Pathologically, there was [illegible]

pericarditis, or both in 17 cases and verrucous endocarditis in 13 A number of different types of vascular lesions were found on microscopic examination. These consisted of simple dilatation of capillary beds, endothelial proliferation in capillaries, arterioles, and venules, and degeneration or necrosis of vessel walls with adjacent thrombosis and hemorrhage A peculiar hyaline thickening of the glomerular tufts was frequently seen and these authors designated this change as the "wire-loop" lesion

Two years later, Denzer and Blumenthal (53) introduced the concept that SLE was a systemic disease not merely of blood vessels but of the derivatives of mesenchyme Later studies by Klemperer, Pollack, and Baehr (146) led them to the conclusion that the fundamental changes in SLE were manifested primarily in the collagenous tissues of the body, and that the widespread visceral lesions could be identified as local manifestations of the basic connective tissue alteration In 1939, Reifenstein and co-workers (210) presented an analysis of cases reported in the literature under a variety of titles, but presenting what seemed to be a common symptom complex characterized by fever, polyarthritis, polyserositis, endocarditis, erythematous cutaneous lesions, nephritis, anemia, and a remittent course. The title of this paper was, "A variable symptom complex of undetermined etiology with fatal termination including conditions described as the visceral erythema group (Osler), disseminated lupus erythematosus, atypical verrucous endocarditis (Libman-Sacks), fever of unknown origin, and diffuse peripheral vascular disease (Christian)"

Perhaps the most important advance in the development of our knowledge of this disease was the discovery of the L E cell (97) This is apparently a specific feature of SLE which enables the diagnosis to be made with certainty in the majority of cases

III PATHOLOGY

In the 50 years after 1872 when Kaposi first described cases of SLE, the autopsy material presented in the literature provided no significant advances in our knowledge of the disease, as the specific lesions were overlooked and death was usually attributed to intercurrent pneumonia or tuberculosis The report of Libman and Sacks in 1924 was the first description of certain of the pathological changes in SLE Subsequently, Gross, Baehr, Klemperer, and Schifrin (5, 93, 144, 146), Jarcho (127), Ginzler and Fox (78) and Denzer and Blumenthal (53), among others, made significant contributions

a. *Vascular Lesions*

Baehr, Klemperer, and Schifrin (5) described vascular lesions throughout the finer ramifications of the systemic [illegible]
varied fror [illegible]
lesions of [illegible]
sociated with thrombi obstructing the lumen Also noted were degenerative and necrotizing lesions in the wall of such vessels associated at times with thrombosis and hemorrhage into adjacent tissues Most characteristic was the peculiar

hyaline thickening of the capillary walls of the glomeruli which they designated as the "wire-loop" lesion

Klemperer, Pollack, and Baehr (146) described the pathological changes in 35 cases and pointed out that the alterations noted in the various organs must be regarded as manifestations of a single process involving the connective tissues of the body The supporting tissue involved may be in the heart, the glomeruli, the skin, or in blood vessels which may in turn affect the function of any organ in the body The primary change was thought to occur in fibroblasts and in the ground substance These authors stressed the fact that a differential point between rheumatic fever and SLE is that in the latter disease, the alteration is predominantly a degeneration of fibroblasts whereas in the former, proliferation of fibroblasts resulting in Aschoff body formation is dominant. In distinguishing between SLE and periarteritis nodosa, they stated that the changes in the connective tissue in the latter disease are accompanied by a conspicuous inflammatory reaction in which participation of eosinophils is usually noteworthy. As a rule, in periarteritis, the vessels of larger caliber suffer the greater damage while small vessels and capillaries may occasionally be affected. They point out that the converse is true in SLE (Fig. 1 A)

b. "Fibrinoid Degeneration"

Klemperer and his colleagues concluded that the morbid process in SLE revolved about a well-defined disturbance of collagen which may affect all organs and tissues of the body The essentially degenerative nature of this disturbance is expressed in its most striking form by the term "fibrinoid degeneration". They stated that this disease process represents a profound physico-chemical alteration of collagenous tissues While "fibrinoid degeneration" may be the most spectacular expression of this alteration in routine stains, the disturbance may also manifest itself in sclerosis of collagen which is particularly evident in the splenic lesions The alteration termed "fibrinoid degeneration", which has been applied to changes in collagenous tissue, is usually characterized by brilliant eosinophilic staining in the hematoxylin eosin preparations, metachromasia, positive silver staining, and positive staining for fibrin This lesion remains a non-specific and little understood reaction which may be noted in a variety of other conditions. In these the alteration is usually sharply localized and identified with obvious direct tissue injury which may be caused by bacteria, toxins, vascular impairment, or a hypersensitivity reaction

c. Hematoxylin Bodies

In 1932 Gross (92) reported the presence of clumps and packets of hematoxylin-staining bodies in the cardiac lesions of cases of Libman-Sacks disease He was of the opinion that these conglomerate masses were derived from nuclear material and that they were specific in nature (Fig. 1 B) Further description of these lesions was made by Ginzler and Fox (78) in 1940. Since that time they have been noted in lesions of many organs in SLE including the heart, lymph nodes, kidney, lung, and spleen but always in tissue of mesenchymal origin.

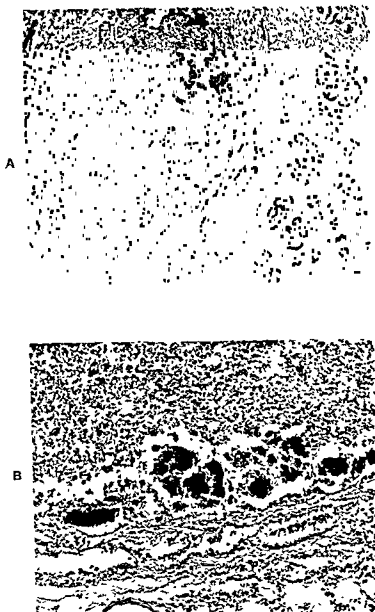


FIG 1 A An acute necrotizing lesion in a vessel in the submucosa of the stomach in a patient with SLE In contrast to the lesions of acute periarteritis nodosa, eosinophils are rare in the cellular exudate about this vessel B Conglomerate masses of hematoxylin bodies in lymph node sinusoids

Klemperer (143) found hematoxylin bodies in 41 of 45 cases of SLE studied histologically. Microscopic analysis has shown that these bodies arise from an alteration in the nuclei of cells which are exclusively of mesenchymal origin such as fibroblasts, histiocytes, endothelial cells, lymphocytes, and polymorphonuclear leucocytes. They are reddish-purple in the hematoxylin-eosin preparations, and are free of any distinctive structure. The single bodies described by Gueft (94) are of cell size while the larger aggregates may be several hundred microns in diameter, and may compose the largest part of a grossly visible structure such as a vegetation on a valve. Studies have indicated that the phagocytized material of the L.E. cell is histochemically similar to the small hematoxylin bodies described. Since L.E. cells are rarely found in autopsy material, although they may occur in a fluid medium such as a pleural exudate or pericardial effusion, it is probable that phagocytosis of this material is uncommon in vivo. Cytochemical studies of interest have been carried out on this material by Klemperer, Gueft, Lee, Leuchtenberger and Pollister (145). Spectrophotometric absorption in the ultraviolet spectrum shows a strong band at 2537 Ångstrom units which is lost after treatment with trichloracetic acid. Digestion with ribosenuclease has no effect, while the Feulgen reaction for desoxyribosenucleic acid is positive. These observations provide evidence that the bodies are derived from nuclear chromatin, and that they contain desoxyribosenucleic acid. Pollister and Leuchtenberger (202) have postulated that the loss of affinity for methyl green together with the relatively strong Feulgen reaction indicates that the nucleic acid is in a depolymerized state. These bodies may be found in areas in which there are other changes in the extracellular portions of the connective tissue such as fibrinoid alteration of the collagen fibers, periarterial fibrosis in the spleen, and increase in metachromasia of the loose connective tissue ground substance. Berman and his associates (23) have also noted the morphologic similarity between these hematoxylin bodies and the L.E. cell inclusions, but they were unable to demonstrate depolymerization in methyl-green-pyronin preparations on bone marrow smears. The observations of Koffler and Markert (148) are of interest in this regard. They noted that ultraviolet radiations, x-ray, nitrogen mustard and peroxides in the presence of eosin produced depolymerization of desoxyribosenucleic acid *in vitro*. While most authors have considered that hematoxylin bodies occur only in SLE, Worken and Pearson have described similar lesions associated with angiitis in the absence of the characteristic changes of lupus erythematosus (273).

d. Involvement of Various Organ Systems

In regard to the frequency with which changes are present at necropsy in the various organs, Klemperer (143) noted verrucous endocarditis in 55%, pericardial lesions in 70%, myocardial lesions in 35%, wire-loop change in the kidney in 60%, focal glomerular loop necrosis in 85% and "onion-skin" lesions in the spleen in 95%. Jessar and his group (129) in 15 postmortem examinations recorded pericardial lesions in seven instances, myocardial lesions in eight, endocarditis in five, splenic lesions in eleven, and focal hepatic necrosis

in four In their series, renal abnormalities were seen in 13 cases, seven being the wire-loop lesion and two renal infarcts Generalized vasculitis was a prominent feature in eight patients, pleuritis in 10, peritonitis in four. In one patient lesions of both lupus erythematosus and dermatomyositis were found at autopsy These figures, which represent only the lesions found after death, are difficult to evaluate in view of the chronic and intermittent course of SLE.

No detailed analysis will be presented of the pathological findings in our series of cases, but appropriate reference will be made to certain of the data in the sections to follow

It is noteworthy that the extent of the morphological changes does not always parallel the severity of the clinical disease at the time of death (43) As is well illustrated in the following case summary, there may be a paucity of anatomical lesions even though the disease runs a very fulminating course.

Case 1

D B (#281005) *This 26 year old colored female housewife entered the hospital July 2, 1953 complaining of a sore throat*

Two weeks before, she noted stiffness in her fingers and wrists with progression to the elbows and knees occurring mostly in the morning There was no swelling, heat or local tenderness One week before, she developed a pleuritic pain in her left chest For one week she had a sore throat She became progressively more lethargic She had fever and was given penicillin and sulfonamides Because the febrile reaction did not subside, she was brought to the hospital for study

On admission she had T 104°F , P 120, R 20, BP 100/60 There was a maculopapular eruption over the cheeks, arms, back and thighs which had an erythematous appearance There was tenderness without swelling or local heat in the middle phalangeal joints, wrists, elbows, hips and knees Fundi showed no hemorrhages or exudates Pharynx was a little hyperemic Small lymph nodes were felt at the angle of each jaw, and in the right supraclavicular and left axillary regions There was tenderness over the thyroid which was not palpable The lungs were clear to percussion and auscultation The heart was not enlarged and no murmurs were noted The liver and spleen could not be felt The uterus seemed normal Rectal examination revealed no abnormalities The neck was supple The cranial nerves were intact, and the deep tendon reflexes were equal and active

During her two weeks in the hospital her temperature varied between 101° and 105° There was a parallel increase in the pulse rate On the second hospital day some enlargement of the cervical lymph nodes was noted, but the evidence of pharyngitis was subsiding and the tenderness over the thyroid had disappeared The following day she complained of [illegible]

of 26,000 Routine stains showed no bacteria On July 7 a pericardial friction rub was heard [illegible]

good bowel sounds and no distention A lumbar puncture on the evening of July 8 revealed faintly cloudy fluid with 350 white cells per cu mm , all of which were polymorphonuclear

cells Routine cultures and those for tubercle bacilli were sterile There was no lowering of the spinal fluid sugar On July 9 she became comatose with short gasping respirations There was periorbital edema and constant twitching of the left side of the face with occasional twitching of the left leg Ptosis was noted of the left lid and the left arm fell limply when raised On that day funduscopic examination showed a soft exudate just beneath the right disc There was cervical rigidity and definite enlargement of the cervical and axillary lymph nodes Crackl [illegible]

peared in the left fundus The white count continued to rise, reaching 25,000, with no significant change in the differential On the day of death, the patient had a generalized convulsion

The blood and spinal fluid STS were negative Serum globulin was 3 gm % and the L E cell test was negative The hematocrit was 29

X-ray of the chest showed a pleural reaction at the left base and what was interpreted to be underlying areas of atelectasis Later, a pleural effusion was noted, and the heart shadow was increased in size

At autopsy no gross lesions were noted other than the pleural effusion Microscopically, there was evidence of pleuritis and pericarditis and foci of necrosis were noted in lymph nodes There was also found the type of pneumonitis seen in systemic lupus However, many sections were searched before any classical lesions of SLE were noted, and they were very few in number Cytoid bodies were found in the nerve fibre layer of the retina.

e *Biopsy and Diagnosis*

Biopsy examination of skin, muscles, and lymph nodes has been widely used for the diagnosis of lupus erythematosus Although changes may be found which are compatible with the disease, particularly when considered along with the clinical picture, pathognomonic changes are unusual

1 Skin. In 1932 Goeckerman and Montgomery (81) evaluated the histological changes in the skin in 26 cases of discoid lupus and 18 cases of SLE. They noted, in comparison, similar changes in the discoid and in the acute type but different in degree The earliest alterations were described as the same in both instances with vasodilatation and edema of the upper layer of the cutis They recommended that biopsies be made from a patch of more than two weeks duration as the earlier lesions are similar to those produced by other cutaneous diseases The acute changes were marked thinning with disappearance of the rete ridges, and intraepidermal or subepidermal vesicles No proliferative changes were noted in the walls of the blood vessels

In the same year Madden (164) also described the histopathological changes in the epidermis This was often thin, and edema of the papillary bodies was so extreme that the epithelium was torn away and bullae arose at the site of rupture Degenerative changes of the collagen and elastic fibers became marked early, and there was homogenization of the connective tissue. Particularly prominent was dilatation of the blood vessels and lymph spaces in both superficial and deep cutis with mild perivascular collections of round cells and a few plasma cells

Montgomery (175) noted that pathologically all transitions from localized discoid to various disseminate types may occur Dilatation of blood vessels and lymphatics was followed by extravasation of leucocytes together with the de-

velopment of relative and absolute hyperkeratosis, keratotic plugging of hair follicles and sweat ducts, acanthosis of the prickle cell layer with adjacent regions of atrophy, *liquefaction necrosis of the basal cell layer, a perivascular, chiefly* lymphocytic, infiltration about the dermal appendages, and destruction of elastic tissue where the infiltration occurred In the acute type dilatation of the superficial capillaries and lymphatics and edema of the cutis with atrophy of the *epidermis and liquefaction necrosis of the basal cell layer became more prominent* and the infiltration usually less marked As the disease progressed atrophic changes occurred in the sebaceous glands and hair follicles Liquefaction of the basal cell layer apparently results from edema of the lymph spaces and may be *so marked as to result in subepithelial or intraepithelial formation of bullae.*

One of the most exhaustive studies of the histopathology of the cutaneous lesions is that of McCreight and Montgomery (169) They made a histologic review of 119 specimens removed for biopsy or on postmortem examination, and *noted the same histologic changes within the epidermis in chronic discoid as in* the systemic or disseminated types, although the degree of change was less pronounced in the disseminated types They stated that it was apparent that no *single pathological change would allow a definite diagnosis of lupus erythematosus However, a combination including hyperkeratosis without parakeratosis,* keratotic plugging of hair follicles, liquefaction degeneration of the basal cell layer, edema of the cutis, dilatation of the superficial capillaries, a cellular infiltrate composed primarily of lymphocytes and the absence of obliterative or proliferative changes in the walls of the deeper blood vessels would *certainly* suggest the diagnosis (Fig 2)

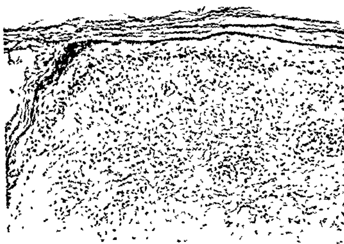


FIG 2 Biopsy of skin from a patient with SLE Hyperkeratosis, vacuolar degeneration of basal epithelial cells, and inflammation, especially perivascular, are all typical of lupus erythematosus

A

B

FIG 3. Lymph node biopsies from a patient with SLE A This section shows an area of fresh necrosis This lesion is not specific for but very suggestive of acute SLE B This section is from a lymph node biopsy in the same patient taken one week after starting treatment with ACTH. There is an area of recent healing necrosis with a border of foam cells.

It was noted by Jessar and his co-workers (129) that in many instances the diagnosis could not be made from skin biopsy in patients who later developed classical manifestations of the disease In sixteen patients in whom the diagnosis was confirmed at autopsy, nine had had skin biopsies of which only three were positive Bundick and Ellis (34) sent a questionnaire to leading dermatological pathologists who indicated that a positive diagnosis could be made in 75 per cent of the cases with skin biopsy This may be true if all other information is considered along with that obtained by histological examination of a cutaneous lesion

2 Lymph nodes When taken in conjunction with the clinical picture the changes noted in lymph nodes removed by biopsy may be of help in diagnosis Ginzler and Fox reported a case in 1940 (78) showing extensive changes in lymph nodes The earliest lesions consisted of foci of cellular necrobiosis with virtually no reactive inflammation These progressed to larger areas of necrosis with complete cell degeneration, disintegration, and pyknosis In many of the areas, some cells *underwent a pinkish-blue granular degeneration* of the cytoplasm with pyknosis apparently coalescing to form striking bluish-violet staining masses resembling calcium in hematoxylin-stained material In retrospect, these were probably large aggregates of "hematoxylin bodies" As the lesion progressed, foam cells appeared at the margins with subsequent scarring at the junction of necrotic and viable tissue Specific epithelioid cell formations did not develop and giant cells were not seen (Fig 3) Such lesions must be distinguished from those of "cat-scratch" disease, acute tularemic necrosis, histoplasmosis and, perhaps, from those of unusual cases of glanders, lymphopathia venereum, tuberculosis, sarcoidosis, brucellosis, and Hodgkin's disease In two cases in the present series the lymph node changes were diagnosed as Hodgkin's disease in one and reticulum cell sarcoma in the other Later developments made it clear that these patients had SLE

3 Muscle Madden (165) studied muscle biopsy specimens in 32 cases with dermatomyositis and lupus erythematosus *A nodular myositis was seen in six* of 21 specimens from patients with lupus erythematosus The lesions were striking in only one who also had rheumatic fever Their conclusion was that the muscle changes in dermatomyositis and lupus were non-specific and similar changes occurred in rheumatoid arthritis, rheumatic fever, scleroderma, thyrotoxicosis, and a variety of other disorders Lowman (162) studied serial sections of muscles from 15 cases with lupus Slight to moderate degenerative changes were noted in 73%, while 37% of 30 control cases showed similar changes He also noted a vascular pattern on the venous side of the circulation composed of edema, cellular reaction and sclerosis These muscle and perineurovascular *changes were identical with those seen in cases of active rheumatoid arthritis* The author concluded that the polymyositic and perineuritic nodules of lupus erythematosus are identical with those seen in rheumatic arthritis and that both are produced in this vascular pattern of reaction The incidence of focal degeneration of nerves was greater in the cases of lupus erythematosus than would be expected, *but the significance of this was unknown to the author Other observers* have noted an arteritis or phlebitis of the small vessels seen in muscles which

cannot be distinguished with certainty from that seen in periarteritis nodosa and rheumatoid arthritis

It has been our experience that biopsy examination is frequently of little help in establishing the diagnosis of lupus, no specific lesion being detected in patients who are later found to have the disease Thus, in our group of patients, lymph node biopsy was nonspecific in 11 instances and positive in only two. Of 19 skin biopsies only 12 were positive, and only one muscle biopsy in 12 gave information of definitive value

IV. ETIOLOGY AND PATHOGENESIS

a Infections, Including Tuberculosis

Since the first description of SLE there has been much speculation about etiology. Most of the arguments, however, are based on no solid evidence. During the early years of this century, one group, mainly German, believed that the disease was associated with tuberculosis and this view dominated the literature until the detailed analysis of Keil (137) showed that it was untenable Other observers thought the basis for the disease was a septicemia probably due to the staphylococcus Detailed bacteriological studies have given no support for this thesis. The disease is associated with a frequent incidence of complicating infections, particularly pneumonitis, and active tuberculosis may develop during the course of the illness In 1941, Kelvin (141) expressed the opinion that lupus was due to an innate characteristic of the skin, probably congenital, which rendered it peculiarly susceptible to the action of tuberculotoxin. His conclusion was based on the result of tuberculin testing in a series of 148 cases of lupus and of 240 individuals with healthy skins or other dermatological conditions. Among recent articles relative to the possibility of infection as an etiological agent is that of Welsh (270) This author described the characteristics of streptococci isolated from the nasopharynx, infected tonsils, apices of infected teeth, and blood of 16 patients with lupus erythematosus Similar, but not identical, streptococci were isolated from patients with pemphigus, dermatitis herpetiformis, and erythema multiforme Moolten and Clark (177) claimed to have isolated a virus from the blood of patients with SLE, but this work has not been confirmed by others

b. Endocrine Factors

Certain evidence has suggested a possible endocrine factor in the pathogenesis of SLE Baehr, Klemperer, and Schifrin (5) noted the high incidence of SLE in females, and Rose and Pillsbury (221) cited the frequency with which the disease affects females within the active sexual phase of life The latter authors described the effects of castration or natural menopause upon the course of SLE in six cases and emphasized the desirability of further investigation of gonadal function Koets (147) followed the 17-ketosteroid output in a patient with SLE and showed that during the chronic untreated phase she excreted amounts as large as followed the administration of ACTH at a later stage The author concluded that the ketosteroid excretion in untreated rheumatic disease expresses the degree of automatic defense the body can develop at a given stage

c Allergy or Hypersensitivity

Evidence has accumulated to indicate that certain types of angiitis are the result of anaphylactic hypersensitivity. However, in many cases of polyarteritis which spontaneously develop in the absence of any allergic reaction to a therapeutic agent, no specific antigen to which the patient is sensitive can be discovered The possibility of an allergic background as the cause of SLE is even less clear That the disease may develop in its acute form following reaction to a foreign protein or to a drug does not constitute sound evidence for an allergic etiology. Rich (213) believes that anaphylactic hypersensitivity probably plays an important role in polyarteritis nodosa, rheumatic fever, SLE, and rheumatoid arthritis Rich and Gregory (217) found in rabbits subjected to protracted anaphylactic reactions of the serum sickness type lesions which were compatible with the sclerosis of the branches of the coronary arteries seen in rheumatic fever and also in SLE They pointed out that there are a variety of reactions seen in the latter disease which are also characteristic of the serum sickness type of anaphylaxis, including fever, cutaneous eruptions, purpura, arthritis, necrotizing inflammatory arterial lesions, focal collagen degeneration, focal necrosis of lymph nodes and spleen, myocarditis, valvulitis, sterile inflammation of serous membranes and sterile pneumonitis Fox (72) has reported a case of SLE developing after the administration of tetanus antitoxin Stokes, Beerman, and Ingraham (246) suggested that SLE is produced by an infectious-allergic mechanism leading to vascular allergic manifestations

Teilum believed (250) that the hyperglobulinemia, periarterial fibrosis of the spleen, and "wire-loop" lesion of the glomerulus in SLE are all expressive of a primary allergic "hyperglobulinosis" of the reticulo-endothelial system He stated that the various phases of the tissue injury, such as "fibrinoid" degeneration with immigration of cells, granuloma formations, and fibrosis as well as primary necrosis can be followed most distinctly in the lungs where they represent a focal allergic pneumonia

Some observers have suggested that the widespread use of chemotherapeutic agents may be correlated with the supposed increase in the incidence of SLE, periarteritis nodosa, and other connective tissue diseases Gold (82) reported eight patients with acute or subacute SLE all of whom had lesions of the skin and photosensitivity In seven of the patients sulfonamide or penicillin therapy had preceded the onset, and in four there had been a sensitivity reaction to one of these drugs It seems likely, in our opinion, that these drugs may act as a trigger mechanism for activation or intensification of the disease, and have no etiological relationship In a recent article Gold and Gowing (83) stated that an antigen-antibody reaction may be the basis of SLE while discoid lupus may represent a cutaneous reaction denoting hypersensitivity to an infective focus These two processes may occur independently or together

d Relation to Other "Collagen" Diseases

Banks (10) and others have grouped together a variety of disorders affecting connective tissue including rheumatic fever, rheumatoid arthritis, lupus ery-

thematosus, periarteritis nodosa, dermatomyositis, and scleroderma. Because of the occurrence of "fibrinoid" degeneration of collagen these observers assumed that the diseases may have a common etiological background. Baehr and Pollack (6) pointed out that connective tissue is the supporting and cementing framework of all organs and tissues and consists essentially of collagen laid down in fibrils and of a ground substance. They suggested that it has only three basic ways of reacting to injury: degeneration, fibrosis, and cellular reaction. "Fibrinoid" degeneration may occur in any type of connective tissue injury, according to these authors, and is not specific for any one type. They believed that "fibrinoid" degeneration of collagen is not a pathological process reliable as a common denominator for the classification of disease. They stated that SLE and diffuse scleroderma have this morphological expression in common, but are so dissimilar clinically that they seem related neither to each other nor to rheumatic fever, rheumatoid arthritis, serum sickness, periarteritis nodosa, or thromboangiitis obliterans in which similar collagen changes may occur.

Ehrich (62) believed that in these various diseases there is production of an abnormal gamma globulin which circulates in the blood and produces injury to mesenchymal tissues. When this is severe, there may be an increase in certain substances released from the damaged tissues and appearing in the blood such as mucopolysaccharides, non-specific hyaluronidase inhibitor, alpha globulins, and fibrinogen. He proposed the term "dysgammaglobulinemia" to designate this group and also included primary amyloidosis and para-amyloidosis in this category.

Certainly it may be said that the etiology of SLE remains a mystery. A variety of stresses including infection, exposure to sunlight and to cold, various allergic reactions including those to therapeutic agents, trauma including minor surgery, and other situations are recognized as being possibly important trigger mechanisms or aggravating factors enhancing the activity of an underlying process.

V. GENERAL CONSIDERATIONS

a. Classification

Classification of reported cases of lupus erythematosus is difficult; because in many articles the clinical features are not stated clearly, and because no standard system of nomenclature has been followed. The terms acute and disseminated, which now imply systemic involvement, have been applied in the past as descriptive terms to cutaneous lesions, there being in many instances no evidence of systemic disease on the basis of the observations reported. Most attempts at classification have been based on the nature of the dermatological manifestations.

A frequently quoted classification is that of O'Leary (188) which divided cases into the following types:

1. chronic discoid
   a. localized
   b. generalized with systemic symptoms usually mild to absent
2. subacute disseminate

3 acute disseminate

Urbach and Thomas (260) have proposed a different scheme as follows.

1. chronic group
   a discoid erythematodes
   b disseminated erythematodes
2 exacerbated group
   a discoid with acute or subacute exacerbation
   b disseminated with acute or subacute exacerbation
3 acute group
   a acute
   b subacute

Many subtypes of the chronic discoid variety have been described, being named in accord with some prominent presenting feature such as lupus erythematous nodularis, verrucosis, etc

Wilson and Jordan (271) investigated the mode of onset of the subacute and acute disseminated forms of L E with particular reference to the interrelationships of the various morphological cutaneous types to the underlying systemic disease process They analyzed 265 cases of disseminated lupus erythematosus with associated cutaneous manifestations Among these were 96 subacute and 169 acute cases which fell into one of three groups In Group I, in general, the muco-cutaneous lesions were acute and often widely disseminated. The interval between the onset of the dermal lesions and the development of systemic manifestations was usually short In Group III the lesions were of the chronic inflammatory type, and associated with a longer interval between the occurrence of the cutaneous lesions and systemic involvement In Group II the lesions were of an intermediate type, occasionally showing atrophy, and associated with an interval of intermediate duration between onset of the cutaneous lesions and systemic involvement.

Attempts to classify the disease into acute and subacute categories other than with reference to the course of the skin lesions serves no useful purpose It is well-known that the course of the disease tends to vary from moment to moment as far as severity is concerned, and the "acuteness" of the illness merely denotes the severity of the constitutional manifestations present at any one period Arnold (3) and Haserick (103) advocated the term "systemic lupus erythematosus" in referring to the generalized form of the disease, and reserved the terms discoid and disseminate to describe the skin lesions This seems the preferable use of terms at the present time The clinical picture presented by this disease, SLE, of which in our opinion the skin lesions whether chronic or acute are only a part of the same process, is so varied in its manifestations and course that no simple classification of clinical types is feasible

b Incidence

The exact incidence of SLE is obscured by the fact that many cases have doubtless gone unrecognized It is not possible to determine whether the disease is now occurring more frequently, although a number of observers feel that it is

The development of the L.E. cell test has led to detection of many cases previously regarded as having other disorders. There is general agreement that SLE can no longer be regarded as an unusual disease entity. Dubois (56) reported that at the Los Angeles County General Hospital the disease was diagnosed in only 11 patients from 1948 through 1949. During the following two years, when an active search for new cases was under way utilizing the L.E. cell test, the diagnosis was made in 44 cases. However, these figures cannot be interpreted as indicating any change in the incidence of the disease.

c. Sex, Race, and Age

Of 23 cases reported by Baehr, Klemperer, and Schifrin (5), 22 were females. With the advent of the newer diagnostic tests, the disease has been recognized with somewhat greater frequency in males and numerous cases have now been reported in Negroes. Reported figures as to sex, race and age of onset are given in Table I. Only recent articles are quoted because of the newer methods of diagnosis. Among these it is seen that females predominated in all series. The peak incidence was in the second, third and fourth decades, but the age at onset ranged from two to 67 years. In general, the racial distribution was similar to that of the particular hospital population concerned.

Montgomery and McCreight (176) compared a large series of cases seen at the Mayo Clinic before 1938 with another observed since that year. They divided the cases into three categories: acute, subacute, and chronic. They noted an increase in the percentage of females in the latter series, but no significant change in the age at onset.

In *Chart 1* is seen the age, sex, and race distribution in our own series of cases.

d. Familial Occurrence

More than one member of a family may be affected with lupus erythematosus. Legobbe (157) compiled a series of such reports by various authors describing the cutaneous lesions in more than one member of a family. Most were siblings. In one family there were eight cases, and in another, four. There was no statement as to systemic manifestations. The author reported three cases of lupus in the members of three families of common descent. Jaworowska (128) described discoid lupus erythematosus in three sisters. Sequeira (231) presented cases of

TABLE I

Systemic lupus erythematosus, age at onset, sex, and race incidence

Authors	*Jessar* (323 cases)	*Dubois* (62 cases)	*Shearn & Pirofsky* (35 cases)	*Present Series* (138 cases)
% Females	85	89	91	78
% White race	91	47	—	84
Age onset				
Average		27 yr		29 yr
Peak	84% (10–40 yr)		56% (over 30 yr)	80% (10–40 yr)
Range	5.5–60 yr	2–67 yr	3–56 yr	5–73 yr

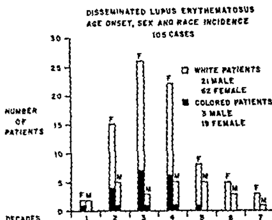


CHART 1 Age at onset and the sex and race incidence in 105 cases of SLE

two sisters with the disease Both children suffered from blueness of the extremities during the winter months and one had albuminuria Shearn and Pirofsky (234) noted SLE in two members of the same family, and Davis and Gutridge (52) reported its occurrence in identical twin sisters.

c. Predisposing Factors

It has long been observed that a number of factors have an apparent relationship to the onset or exacerbation of the cutaneous or other manifestations of this disease Among the most prominent of these which have been commented upon in recent reports are exposure to sunlight or ultraviolet rays, the presence of focal infection or reaction to foreign protein including tuberculoprotein, reaction to a variety of therapeutic agents including gold, sulfonamides and penicillin, and finally emotional trauma

Focal infections, for example, were noted in essentially half of the patients observed by Shearn and Pirofsky (234) Jessar and his co-workers (129) found no relationship of the disease to upper respiratory infections but noted that sensitivity to sunlight was a precipitating factor in 27% of their cases. In many reports there was a frequent story of the use of sulfonamides or other antibiotics but no clear evidence of a temporal relationship to onset Gold (82) presented a study of eight patients with acute or subacute disseminated lupus, all of whom had lesions of the skin and sensitivity to sunlight In seven, sulfonamide or penicillin therapy had preceded the onset, and in four there was a history of a sensitivity reaction to one of these drugs Many observers have felt that any allergic type of reaction was purely coincidental or, perhaps, responsible for a flare-up of the disease after its onset Another view was that allergic reactions are an intrinsic manifestation of the disease process This is a difficult point to decide since only recently has it been possible to reach a reasonable conclusion as to the initial manifestations of this disease, and to determine the time of its onset with accuracy.

Slocumb (238) has stated that patients with rheumatoid arthritis who have

developed chronic hypercortisonism may exhibit during hormone withdrawal a panmesenchymal and panangiitic reaction If the reaction is severe there may be fever, pericarditis, pleurisy, signs of pulmonary consolidation, renal involvement and hypoalbuminemia In 15 patients the L.E. cell test was positive and in four there was a false positive serologic test for syphilis Since it is not uncommon for exacerbation of SLE to occur during withdrawal of cortisone administration, it seems most reasonable to assume that these patients had this disease which had previously been manifested by arthritis alone

Prolonged administration of hydrazinophthalazine in the treatment of hypertension has been followed in some patients by a syndrome which resembles SLE (60, 182) Manifestations included fever, arthritis, polyserositis, and pneumonitis In several instances the L E cell test gave positive results. The significance of these observations remains to be clarified, but as will be discussed later hypertension is uncommon in patients with SLE In a recent article, Perry and Schroeder (196) noted this complication in 8 1 per cent of 211 patients who had received treatment for two to 22 months, the total amount of the offending agent ranging from 25 to 350 grams The fully developed picture resembled SLE, according to the authors, but in only one case were L E cells found.

Most of the patients in our own series had excellent general health prior to the onset of SLE Several of them, however, had a history of antecedent chronic or recurrent upper respiratory infections, including sinusitis and tonsillitis, but this group is too small to have significance.

The incidence of various clinical manifestations of allergy was carefully sought in our patients While a wide variety of allergic phenomena frequently occurred after the disease had made its appearance clinically, they were not common prior to that time (Table II) It was as if the development of SLE gave rise to a state of altered reactivity which was then associated with the frequent occurrence of allergic phenomena

Repeated acute exacerbations of SLE followed drug reactions which seemed to serve as trigger mechanisms for a series of events which sometimes terminated in the patient's death In certain cases it appeared that a particular drug or other allergic reaction initiated the disease process, but usually close analysis of the history revealed the prior existence of symptoms. From the therapeutic standpoint, patients with lupus should be given drugs or other agents likely to induce an allergic reaction with even more caution than in individuals without this disease The following case summary illustrates these difficulties This patient had a long illness and was told repeatedly that she had an "allergy" In retrospect it is probable that she had chronic SLE with remissions and relapses

Case 2

M C (#641028), a 42 year old white school teacher, entered in May, 1953 complaining of generalized edema of 10 months' duration At age 13 she developed parotid swelling ac- [illegible] ear
at
d
d
d
with periorbital edema and conjunctival injection At age 34 she had [illegible]

TABLE II

Allergic manifestations in systemic lupus erythematosus
(Present Series—105 Cases)

	Before Diagnosis	After Diagnosis
Urticaria—usually attributed to food	11	None
Hay fever	2	None
Contact dermatitis	1	None
Drug reaction*		
ACTH	None	4
Penicillin	2	6
Sulfonamides	1	5
Streptomycin	None	3
Chloramphenicol	None	2
Gold	2	4
Quinine	1	
PABA	None	1
Aureomycin	None	2
Others	No data	8

* Frequently resulted in severe exacerbation of the lupus erythematosus persisting long after cessation of drug administration In three instances patient sensitive to two or more drugs

with arthralgia thought due to fish One year later she was told she had virus pneumonia on four occasions during a four month period She was critically ill with fever, malaise, myalgia, arthralgia, underwent several thoracenteses, and had pericarditis At age 38 she had parotid swelling associated with local inflammation and pus was evacuated into the buccal cavity She developed facial edema following the administration of sulfonamide From this period on her strength progressively declined She had several episodes of "flu" each year characterized by fever, malaise, myalgia, and arthralgia One year before admission she noted onset of dependent edema associated with swelling of her face She noted blueness and numbness of her fingers on exposure to minimal cold Six months later she had swelling about the eyes associated with a scaly, erythematous eruption Edema progressed and alopecia developed

On admission, the temperature was 101°F (R), pulse 90, respirations 24, blood pressure 115/65 She appeared chronically ill and had anasarca The skin was dry, scaly, and thickened In the periorbital areas there was edema and the skin was erythematous and scaly. The finger tips were atrophic The mucous membranes were pale Cytoid bodies were noted in the fundi There were palpable cervical and axillary lymph nodes Medium râles were heard at both lung bases A soft systolic murmur was noted to the left of the sternum The liver was palpated two finger-breadths below the costal margin There was ascites There was slight swelling of the fingers, but otherwise no objective evidence of arthritis although she complained of pains over many joints

There was no anemia The white cell count was 8,000 with a normal differential Serum albumin was 1 9 gm %, globulin 3 gm % X-ray of the chest revealed a pleural reaction on the right with some fluid Tests for L E cells were positive on several occasions Electrocardiogram showed sinus tachycardia, low amplitude of the QRS and T waves These [illegible]

lowered to 100 mg a day and her weight was 114 lb

VI. THE CLINICAL MANIFESTATIONS OF SYSTEMIC LUPUS ERYTHEMATOSUS

a General Considerations

The picture of the disease at onset may assume a wide variety of patterns A single organ system may be involved such as the skin, joints or kidneys, or several systems may be implicated The skin and joints are most frequently affected singly, but any of the organ systems may be, suggesting that the patient has a localized disorder rather than a generalized process The following is a list of diagnoses made by various physicians who saw our patients during the early stages:

1 Rheumatic fever
2 Rheumatoid arthritis
3. Other disorders involving the skin
4 Latent syphilis
5 Idiopathic thrombocytopenia
6 Anemia due to other causes
7 Leucopenia due to other causes
8 Pleurisy due to other causes
9 Virus pneumonia
10 Raynaud's disease
11 Fever of unknown origin
12 Acute nephritis
13 Epilepsy
14. Acute psychosis
15 Drug reaction
16 Septicemia
17 Dermatomyositis
18 Lymphoma
19. Scleroderma
20 Tuberculosis
21. Trichinosis
22 Brucellosis
23 Bacterial endocarditis
24. Functional illness

The initial manifestations may be so vague that it is difficult to be certain when the disease has actually begun The patient may state, for example, that she "has always been sensitive to the sun" or has had recurrent mild aching in joints since childhood Often the patient does not appreciate the connection between the present illness and some isolated incident in the past, such as pleurisy or a skin eruption, and fails to report it The observer may be uncertain whether a particular past incident such as an episode of pneumonia or an outbreak of hives was due to SLE Table III is a summary of the initial manifestations of 105 of the patients in our series

As pointed out by Ross and Wells (223) the more important manifestations of the systemic disease were adequately described in the older literature, but many of these early reports are capable of interpretation only in the light of recent knowledge Many cases, until the advent of the newer diagnostic tests, were unrecognized or were diagnosed according to the major presenting difficulty such as rheumatoid arthritis In many with dermatologic manifestations, little attention was paid to such systemic symptoms as fever, malaise, weakness, fatigue, loss of weight, and arthralgia

Edema is a frequent finding and may be focal or diffuse. Skin lesions may appear early or late or not at all during the entire course of the illness There is no classic pattern of the disease, although a large percentage of the patients have joint or cutaneous manifestations, as well as constitutional difficulties with fever, fairly early in the course of the illness.

TABLE IV—*Continued*

	Number of Patients			
	Harvey et al (105)	Dubois (62)	Jessar et al (44)	Shearn & Pirofsky (34)
l—total				
	14	36		{50
	11	40	{18	{27
	8	21		
ge	5			
l pain	10	37	22	35
gn	6			
		24		15
urinary				
l—total (Some abnormality such as albuminuria, abnormal sediment)	65	57	70	62
al (mild)	39			
(moderate-severe)	23			
(uremia)	11		16	
Menorrhagia	14			
Central nervous system				
Psychoses	13	23	9	
Convulsions	17	31	7	15
Hemiplegia	2		2	
Biological false positive STS*	15	33	28	19
Positive skin biopsy	11 (of 19)	52 (23)		
Positive lymph node biopsy	1 (of 13)			
Positive muscle biopsy	1 (of 12)			
Leucopenia (1 count below 4,500)		63	70	74
Anemia (below 11 gm)	78	78	95	97
Thrombocytopenia	26	10		31
L E cell test (% positive, no performed)	82 (96)	69 (60)		94 (31)

* These were not proven by the treponema immobilization test They indicate positive tests of the routine type which were of low titre in the absence of definite history of or lesions pathognomonic of syphilis

observer must search the background for past illnesses which might be related A present occurrence may gain meaning from what has happened in the past

The disease may appear with a confusing array of manifestations resulting from multisystem involvement in which it is difficult to detect any obvious continuity Joint, and with somewhat lesser frequency, muco-cutaneous manifestations are commonly present in episodic fashion and are helpful in pointing towards the correct diagnosis

The following case history with a number of isolated episodes involving various organ systems, and the final diagnosis of SLE made only after many years, illustrates some of the features discussed above

Case 3

L W. (#240496), a 49 year old colored female, was admitted for the fourteenth time on ctober 3, 1953 Except for mild hypertension and slight albuminuria with pregnancies she

TABLE IV

Percentage incidence of certain manifestations of systemic lupus erythematosus

	Number of Patients			
	Harvey et al (105)	Dubois (62)	Jessar et al (44)	Shearn & Pirofsky (54)
General				
Weight loss	71	82	100	74
Fever	86	97	95	100
Skin				
All types	85	52	68	91
Butterfly	39	43		
Photosensitivity	11	40		58
Pigmentation	12	16		
Purpuric	9	—		15
Mucosal	14	11	18	
Hives	7	—		
Alopecia	3	51		
Raynaud's	10	26	16	6
Joints				
Arthritis and arthralgia	90	90	77	85
"Typical rheumatoid" with deformity	27	31		12
Lymph nodes				
General enlargement	34	42	37	68
Localized enlargement	24			
Splenomegaly	15	8	27	41
Hepatomegaly	32	34	29	44
Jaundice	3	11		12
Eye grounds—total	30	32	20	28
Cytoid bodies	24			
Hemorrhages	10			
Exudates	5			
Lungs				
Pleurisy	56	60		50
with effusion	16	55	39	24
Pneumonia, lupus	22		20	
bacterial	23			
Cardiac				
Total incidence	52	—	70	
Enlarged heart	15		34	
Cardiac failure	8			24
Systolic murmur	44	42	55	71
Libman-Sachs lesions	12 (of 38 autopsied)			
Pericarditis	45	44	23	18
Myocarditis (incl gallop rhythm)	16 (of 38 autopsied)	18		21
Hypertension	14		18	32
Conduction defects	5			

Dubois (56) noted that arthritis was the most common presenting feature in his 64 cases, being the initial manifestation in 34 per cent The picture was usually typical of early rheumatoid involvement and in most acute cases there was arthralgia of the proximal interphalangeal joints as well as of the elbows, knees, and ankles In his cases fusiform swelling of the proximal interphalangeal joints was common in the exacerbations of the disease, and a persistent deformity was described in 30 per cent He observed, as have others, that patients may complain of arthralgia, with or without joint swelling, for many years prior to any other evidence of systemic involvement.

Lowman (162) examined the synovial tissues pathologically in five patients with SLE coming to autopsy and noted that the vascular changes were identical with the pattern of reaction seen elsewhere The stroma showed edema initially and subsequently fibroblastic response with ultimate fibrosis The synovial lining cells only occasionally showed hyperplastic changes He stated that the vascular reaction was similar to that seen in active rheumatoid arthritis In a patient who had had classical rheumatoid arthritis for many years, recently autopsied in the Johns Hopkins Hospital (autopsy #21097), the typical histological changes of that disease were described including massive rheumatic nodules showing collagen degeneration Also seen were typical lesions of lupus erythematosus in the spleen and heart

Bennett and Dallenbach (20) studied at autopsy the synovial membranes from two untreated cases The synovial tissues revealed remarkable deposits of fibrin upon and within the intima Other morphologic evidences of inflammation were almost absent "Fibrinoid" change in synovial and sub-synovial connective tissue was also observed in scattered areas These two patients died after illnesses of 29 and 10 months and had revealed similar alterations clinically with persistent arthritis After this long period of arthritis there were no adhesions across the joint clefts and pannus had not developed at the perichondral margins of the cartilage surfaces The cellular components of the inflammatory exudate were minimal, and the changes were thought to be unlike those of rheumatoid arthritis

In a group of 105 of our patients, there were only ten who did not have joint involvement While arthritis may occur at any period during the course of SLE, it was frequently one of the earliest manifestations, and in 63 per cent joint involvement occurred during the initial episode of illness Arthritis was often the sole early manifestation, leading to the misconception that the patient had some other type of joint disease such as rheumatoid arthritis In other instances, the initial episode of arthralgia or arthritis was associated with additional evidences of disease, such as eruption, fever, or pleuritis In patients presenting with arthritis, a long period sometimes elapsed before other typical manifestations of SLE appeared as is illustrated by the following case

Case 4

K L (#464514), a 36 year old white male, was admitted for the first time on January 6, 1950 Twenty years before admission he developed migratory polyarthritis which spontaneously subsided For the subsequent 12 years he was well, at which time a small erythematous patch appeared on his nose When treated with iodine and ultra violet light a

had been well until 1936 when she had an acute pleuritis and developed polyarthralgia attributed to an infected tooth The arthralgia persisted intermittently, but she was relatively well until 1946 when she developed fever, nausea, vomiting and bloody diarrhea A diagnosis of bacillary dysentery was made but not proved, and she recovered over a period of three weeks. In 1949 she complained of exertional dyspnea and because of a mitral systolic murmur and arthralgia, a diagnosis of rheumatic heart disease was made At the same time she developed a cutaneous eruption involving the face and upper trunk which was called "scabies" In June, 1953 she was admitted complaining of abdominal cramps, rectal bleeding and loss of 65 lb in weight over the preceding five years The blood pressure was 160/100, the hematocrit 21, blood STS doubtful and serum globulin concentration 5 gm per cent *Albuminuria was noted and after hemorrhoidectomy she became oliguric for a brief period.* On October 1, 1953 she entered the Gynecological service complaining of crampy pain in the left lower quadrant and bouts of hematuria For four months she had felt weak, had "mild sweats", and "shaking" pains in the chest Her hematocrit was 17, and the NPN 71. The urinary sediment was loaded with white cells and erythrocytes Urine culture showed *Coli aerogenes* L E cells were found in the peripheral blood There was also evidence of myocardial involvement with heart failure

It seems clear that this patient had had SLE for at least 17 years with episodes in which there was involvement of the pleura, joints, heart, skin, intestinal tract, and finally the kidney with renal insufficiency Complicating the last episode was a urinary tract infection After treatment of the infection she was placed on cortisone and has been asymptomatic for several months

b Joint Manifestations

Kaposi (135) observed the occurrence of arthralgia in SLE and noted that joint complaints may precede the fulminating phase of the illness Joint manifestations including arthralgia and arthritis appear in the majority of cases. Reifenstein and his co-workers (210) reviewed 18 cases and noted articular manifestations in all Migratory arthritis was noted in 23 of 30 cases described by Coburn and Moore (43), *while Baehr and co-authors (5) observed joint involvement* in 17 of 23 cases Slocumb (237) described ten patients in whom the joints were acutely painful and swollen with local redness and heat Six of the patients had acute and subacute attacks of swelling, pain and redness of the joints with residual joint swelling, stiffness and pain between attacks One developed a chronic, progressive, deforming arthritis

Much more commonly seen, in our experience, than these striking objective changes is the complaint of arthralgia with mild, soft tissue swelling without redness or much local tenderness.

Friedman, Swartz, Trubek and Steinbrocker (74) stated that the articular manifestations may be classified into three major groups: first, myalgias and arthralgias, second, acute or subacute migratory polyarthritis; and third, chronic progressive polyarthritis with deformity They noted that the cases are often misdiagnosed as fibrositis, rheumatic fever, or rheumatoid arthritis.

Shearn and Pirofsky (234) stated that the migratory polyarthritis seen in this disease may be similar to that of rheumatic fever, and that more than half of their patients had varying degrees of heat, swelling and local redness. Ross *and Wells (223) found the joint changes indistinguishable from those of rheuma*toid arthritis in nine of their 34 cases They stated that advanced destruction of the articular cartilages as seen in rheumatoid arthritis was not frequently demonstrated

migratory in character, though localization in a few joints, particularly the hands, wrists, and knees, also was common. In slightly less than one-half of the patients, the arthritis was characterized by local signs of inflammation, such as redness, swelling, and heat. In the remainder such signs were absent, there being only arthralgia Characteristically, there was a disproportion between the severity of the discomfort and the objective evidences of arthritis Skeletal deformities were frequently associated with chronic arthritic involvement. In 28 of 95 patients with arthritis it was described as typical of rheumatoid arthritis (Fig 4). In some patients contractures, muscle atrophy, and joint deformity (Fig 5) were marked, at times being completely disabling In contrast were individuals who had severe pains for many years without developing disability or deformity. The pain varied greatly in intensity, at times being mild and fleeting, at other times excruciatingly severe so that the patient could not be touched without crying out

Tenderness in the muscles and the periarticular tissues frequently accompanied the arthritis Commonly there was an element of both myositis and arthritis At times there was a marked degree of muscle involvement, manifested by soreness and tenderness of the muscles and less frequently by severe muscle atrophy This was most prominent about the shoulder girdle and the upper extremities In two instances the muscles were so extensively involved that the diagnosis of dermatomyositis was suspected until post-mortem examination in one instance and the discovery of L E cells in the other The pronounced degree of wasting of the shoulder girdle muscles gave rise to the possibility of some type of primary myopathy in a few instances

Spontaneous remission of the joint involvement was common, the arthritis



FIG 4 This patient had had SLE for eleven months Note the symmetrical enlargement of the middle phalangeal joints and the atrophy of the intrinsic hand muscles

florid erythematous eruption appeared on the butterfly area of the face, soon spreading to involve the forearms and shoulders At the same time there was marked myalgia. The eruption persisted, but he was otherwise well until three years prior to admission when he had a febrile illness associated with polyarthritis, diagnosed as influenza He was admitted in January, 1950, because of another recurrence of fever and arthritis, at which time L E cells were found in the peripheral blood and skin biopsy showed changes compatible with lupus erythematosus

During the clinical course of SLE, attacks of joint pains recur episodically, the periods of active joint involvement lasting from a few days to months or even years Several of our patients complained of peculiar fleeting pain in one joint, lasting but a few hours and then disappearing only to reappear in another joint Joint involvement was usually prominent during any period of exacerbation. Stress of various sorts seemed to precipitate this occurrence; for example, heavy exertion, operative procedures, drug reactions, intercurrent infections (commonly of the upper respiratory tract) as is illustrated in the following cases:

Case 5

A G (#495127), a 37-year old white female, was admitted July 29, 1951 When 8 years

sulfonamide for a suspected urinary tract infection following which she developed an acute illness with severe polyarthritis, spiking fever, chills, malaise, weight loss, and weakness *On admission her joints showed changes which were described as being typical of* rheumatoid arthritis L E cells were found in the peripheral blood

Case 6

In 1915 she
from this
until the
time of admission In 1920 she had chorioretinitis Three weeks before admission after unusually strenuous exertion, she developed redness and swelling in her hands, wrists, elbows,
matic
sore
ood
ved
an
Six weeks prior to her second admission she was again given
On
nt
he

Any joint in the body may be involved by the arthritic process of SLE Most commonly implicated in our cases were the hands, wrists, elbows, shoulders, knees, and ankles In several instances the temporomandibular joints and the spine and hips were involved Severe involvement of the spine and pelvic joints at times suggested Marie-Strumpell arthritis The joint pains were most often

ease. He noted that the disease may run its entire course without cutaneous lesions Jessar and his co-workers (129) noted a skin eruption in 84 per cent of 323 patients. The lesions were pruritic in 16 per cent, and a typical butterfly distribution was noted in 43 per cent, in half of whom it was a preterminal manifestation The skin involvement varied from mild erythema to vesicular and bullous lesions with at times erosion, crusting and scar formation

Dubois (56) recorded absence of skin lesions in 16 per cent of his series of 64 cases In the remainder, the dermal manifestations were pleomorphic in character varying from macules to bullous lesions He recognized that involvement in the butterfly area may be transient with a mild erythema lasting for a few days or it may be *chronic extending over a period of years Accompanying it may be* edema of the skin and periorbital tissues resembling angioneurotic edema Scaling may occur and even in the disseminated lesions of SLE, atrophy may take place. With healing, pigmentation may remain and at times leucoderma develops in areas previously the site of cutaneous activity Lesions on the extremities are not uncommon and consist of small erythematous macular areas or erythematous papules scattered over the arms and legs which may ulcerate and heal by scarring On the hands there may be areas of erythematous mottling which blanch on pressure although the lesions may become fixed and at times undergo necrosis This author stated that the most characteristic lesions other than the discoid

Baehr, Klemperer, and Schifrin (5). They stated that at the onset or later in the course of the disease vascular lesions become visible on the skin as erythematous macules or patches which tend to become confluent The erythema may involve the butterfly region and also be present on other areas of the face and neck, particularly those exposed to the sun They also noted the characteristic erythematous changes located on the ends of the fingers, about the nailbeds, on the thenar and hypothenar eminences, and on the terminal portions of the toes and the ball of the foot. Areas subject to friction or mechanical trauma developed erythematous changes and purpuric or petechial areas were often seen within the erythematous patches They noted the pigmentary changes and also the development of shallow ulcers on the mucous membranes surrounded by an erythematous or hemorrhagic areola When viewed under the capillary microscope the involved skin about the nailbed contained many more patent and dilated capillaries than normal which were visible through a hazy film due to the exudation of serum into the subcutaneous tissues This exudation may be sufficient to elevate the corium and result in the formation of small blebs

Keil (139, 140) has written extensively on the morphologic variants in the skin in SLE, their relation to other diseases, particularly upon their differentiation from the lesions of dermatomyositis

Wilson and Jordan (271) stated that in the great majority of cases atrophy does not develop in the acute lesions of disseminated lupus, but that this is not universally true. They reported that, in addition to the pseudo-atrophy due to

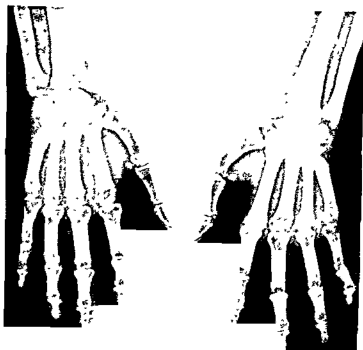


FIG 5 X-ray of the hand in a patient with SLE who had chronic arthritis The osteoporotic changes and the alterations in the carpal areas including narrowing of the joint spaces were interpreted as similar to those seen in rheumatoid arthritis

subsiding for varying periods of time, not infrequently for many years, as already indicated and as illustrated by the following case·

Case 7

H T (#415738) was a 34 year old white female, whose illness began 16 years before admission in June, 1952 with onset of migratory polyarthritis with redness, swelling, and heat which was present intermittently for ten years but left no residual changes in the joints After freedom from pain for six years the lower spine became involved in the "arthritic" process Though she lost 20 lb in weight, she was not aware of fever For an indefinite period, she had had a recurrent erythematous eruption over the butterfly area and the chest as well as episodes of angioneurotic edema Eight years before admission she was found to have a positive STS although there was no history of syphilis Nevertheless, she was given antisyphilitic treatment, following which her joint symptoms became worse

In June, 1952 she was admitted to the surgical service because of pain in the lumbo-sacral spine thought due to a ruptured intervertebral disk L E cells were found in the peripheral blood She was given a course of cortisone with the thought that the pain in the spine might be a manifestation of SLE but there was no response She was operated upon and a ruptured disk was found

c. *Muco-cutaneous Manifestations*

Osler emphasized the polymorphic nature of the skin lesions, and pointed out that dermal involvement is merely the external manifestation of a systemic dis



FIG 6 The typical "butterfly" eruption in this patient with SLE had been present for one year

posure to the sun Reaction to various drugs was also frequently followed by a "lighting-up" of the muco-cutaneous lesions.

Raynaud's phenomenon was present in ten patients In each instance it preceded the development of other manifestations of SLE by many years, and was always associated with arthritis

Ten patients had tender subcutaneous nodules which appeared on the extremities near large joints, and in two instances they were felt behind the ears and over the occiput The appearance of these nodules was always associated with an acute exacerbation of arthritis Purpuric lesions were not uncommon and in 16 instances were associated with thrombocytopenia

In 15 patients the cutaneous alterations were accompanied by mucosal lesions These were almost always within the oral cavity and occurred during an acute episode of the disease, though not necessarily a severe one At times they were erythematous or petechial patches, and at other times herpetic type ulcers developed These were painful, became secondarily infected, and were a source of distress

In 31 patients the cutaneous manifestations of SLE preceded all others, at times by an interval of many years In one instance, for example, there was dermal involvement alone for 14 years

Case 8

A M (#588485) was a 44-year old white female admitted October, 1951 Sixteen years before admission an erythematous eruption had appeared on her back after exposure to the

thinning of the epidermis and stretching due to underlying edema, chronic discoid lesions with true atrophy were observed to develop on sites of previously acute lesions in five cases

Montgomery (175) pointed out that the cutaneous lesions of lupus erythematosus may simulate clinically the [illegible]

are sarcoidosis, psoriasis, pityriasis rubra pilaris, scleroderma, acrocyanosis, dermatomyositis and erythema multiforme Montgomery noted also that the incidence of epitheliomatous change in the chronic lesions of lupus erythematosus is less frequent than in lupus vulgaris, and believed that chronic lupus must not be regarded as a precancerous condition. Epitheliomas have developed usually as a sequel to radiation therapy, and are most often of the squamous cell type.

Subcutaneous nodules were described by Hebra and Kaposi Ross and Wells (223) encountered subcutaneous nodules in two of their 34 patients, and Bennett, Zeller, and Bauer (21) have found such nodules on histologic examination to be indistinguishable from those encountered in r eumatic fever or rheumatoid arthritis.

Lewis (158) has noted that the lesions of lupus erythematosus affect precisely those areas of the skin supplied by "atonic" vessels. These he designated as vessels failing to respond in the normal manner to the intracutaneous injection of epinephrine and posterior pituitary substance. The flush area of the face, the anterior triangle of the neck, the palms and soles, the dorsa of the hands, the ears, and to a lesser extent the buttock are supplied by vessels of this category.

All but 16 of 105 of the patients in our series had some type of cutaneous manifestation during their illness The most frequently involved areas were the face, the neck, the V-area of the chest, the upper extremities, fingers and lower extremities The trunk and thighs were less frequently implicated. The most commonly observed alterations were erythematous, scaling, pruritic lesions which sometimes occurred in patches, at other times coalesced to involve a wide area There was often marked vascularization of the lesions with the development of small telangiectases This was most frequently observed on the face and about the fingers. On other occasions the involved skin had an erythematous blush, often with a violaceous hue This was particularly common on the malar eminences, presenting the classical "butterfly" appearance (Fig. 6).

Of importance to point out is the frequency with which these patients had transient urticaria and edema of the angioneurotic type. Such lesions are frequently not recognized to be manifestations of SLE

In 13 patients alteration in pigmentation was marked, patches of increased pigmentation contrasting with areas of vitiligo In four there was such pronounced alteration of pigmentation and such striking thickening of the skin and subcutaneous tissues, particularly about the hands and other joints, that it was impossible to exclude scleroderma on clinical grounds alone. In four the cutaneous lesions were associated with varying degrees of alopecia Twelve patients stated that their cutaneous manifestations were definitely made worse by ex-

picture, the discoid form may undergo an acute exacerbation with dissemination of lesions and constitutional symptoms, examination of skin biopsy material reveals changes transitional to those encountered in the fixed variety (as in the report by Goeckerman and Montgomery), the exciting causes of the acute phase are manifold including sunlight, ultraviolet light, roentgen rays, exposure to cold, and drug reactions Although these drugs have been used in the treatment of other cutaneous diseases, in none had the clinical course been complicated by a series of phenomena identical with or strictly comparable with those of acute lupus It appeared, therefore, to Keil that the symptom complex typical of acute lupus may appear in the course of the discoid form under the influence of these agents

In the cases reported by Dubois (56) two began as the chronic discoid form One was a male who had had discoid lesions for 18 years at which time dissemination occurred with the finding of L E. cells

The evidence is impressive that chronic discoid lupus may suddenly pass into a stage of acute systemic involvement This course of events took place in three patients in our group, as exemplified by the following case

Case 9

S G (#570399) was a 44 year old colored female admitted in April 3, 1951 For six years she had been treated in the Dermatology Clinic because of chronic discoid lupus involving her forehead and scalp with subsequent loss of hair In all other respects her health had been excellent Six weeks before admission she developed a sore throat followed shortly by fever, acute polyarthritis, pain in the left chest, anorexia, and weight loss She continued to run fever, the temperature varying between 100–102°F and rising to 104–105°F shortly before admission On examination at the time of entry she was acutely ill, complaining of severe pains in her joints She was much underweight There was marked alopecia Dr Lloyd Ketron described typical lesions of discoid lupus on her face There was moderate generalized lymph node enlargement Cytoid bodies were seen in both fundi The heart and lungs were normal While the patient complained bitterly of painful joints, there were no objective changes There was albuminuria, hyperglobulinemia, moderate anemia and slight leucopenia Repeated tests were negative for L E cells However, a lymph node biopsy showed changes compatible with SLE After ACTH administration her temperature returned to normal and the joint pains vanished She gained weight and felt much improved The skin lesions healed slowly

It was frequently observed in our own series that the mucocutaneous alterations first made their appearance or became exaggerated following the administration of certain drugs, particularly heavy metals, the sulfonamides, penicillin, and iodine This same deleterious effect was noted after exposure to the sun, the use of ultraviolet light or the administration of vaccines The stress of an operation or an infection might be followed by the development of an eruption or the spread and exaggeration of one already present

The cutaneous alterations in this disease may be very bizarre as shown by the following case

Case 10

C G (#553829) was a 41 year old white male admitted in October, 1950 with a 10 year history of migratory polyarthritis and five years of generalized swelling, redness and scaling

sun A year later "red spots" were observed on her right cheek She was told that she had lupus erythematosus, and was treated with gold with clearing of the lesions Nine years later the erythematous eruption reappeared on her cheek after exposure to the sun Once again she was treated intermittently with gold salts and the rash appeared recurrently for a period of three years In April, 1951 she was treated with ascorbic acid at which time the eruption became more widespread Two years prior to admission and 14 years after the initial eruption, she had suddenly developed fever and pain in her shoulders and wrists which became red, hot, swollen and extremely painful L E cells were found in the peripheral blood

In forty patients the cutaneous lesions did not develop for varying periods after other manifestations had made their appearance. Thus, in 14 instances five years or longer elapsed between the onset of SLE and cutaneous changes, and in six instances the lapse of time was more than ten years In a smaller number the cutaneous alterations occurred simultaneously with other manifestations, in particular, fever and joint pains.

1 The relationship of discoid LE to SLE. Opinion has varied as to the relationship of discoid lupus to SLE. Belote (19) expressed the belief that the chronic discoid and the acute disseminated forms represent variations of the same disease In contrast is the statement by Baehr (4a) that "in spite of its name this disease (discoid lupus) bears no relation whatsoever to systemic lupus". In the series of 96 patients reported by Wilson and Jordan (271) it was observed that *patients with chronic discoid lupus might develop acute or subacute lupus erythematosus* disseminatus at any time, particularly incident to exposure to the sun, other types of ultraviolet radiation, x-ray therapy, chronic infection or treatment with gold In their patients chronic skin lesions preceded subacute disseminated lupus in 26 per cent and acute lupus erythematosus in 20 per cent. Shearn and Pirofsky (234) observed that six patients exhibited facial eruptions diagnosed as chronic discoid lupus prior to the development of SLE For periods as long as 25 years these lesions remained localized and the patients had no systemic complaints. In the series of Montgomery and McCreight (176) 22 per cent of the patients *with acute and subacute systemic lupus had discoid lesions of* the skin as an early manifestation Montgomery (175) made the statement that in a third of 30 cases of acute disseminate lupus erythematosus, the disease started as the chronic localized discoid type and that pathologically all transitions from localized discoid to various disseminate types of lupus erythematosus may occur

Of interest also is the statement by Rein and Kostant (211) that a high percentage of biologic false positive Wassermann reactions occurred in patients with chronic localized discoid lupus suggesting that it represented a systemic disturbance even when the physical changes were localized to limited areas of the skin.

Keil (139) stated that there is a tendency among internists to regard the acute variety of lupus erythematosus as an independent entity based on two grounds: (1) the frequent absence of atrophy in the cutaneous lesions, and (2) the severity of the clinical symptoms with a poor prognosis in the acute phase. He thought that they probably represent variants of the same disorder, and presented four principal reasons for linking them: there are gradual and progressive transitions between acute lupus and the ordinary chronic discoid variety in the morphologic

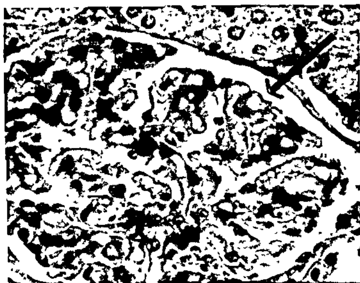


FIG 7 Glomerulus showing the "wire-loop lesion"

Specific vascular lesions may be difficult to find even in patients who have classical fulminating SLE at the time of death

Stickney and Keith (244) studied 15 cases of SLE in which renal lesions were present In four the disease terminated in uremia with a blood urea of more than 60 mg % In these patients as in five others there was albuminuria, microscopic hematuria, and cylindruria All of the cases studied by these authors showed good renal function until the final stages of the disease The most definite lesion was a proliferation of the endothelial cells of the glomerular capillaries Hyaline thickening of capillary walls and an irregularity and thickening of the basement membrane were also observed In one case there were pathologic changes characteristic of glomerulonephritis and in one, evidence of subacute or early chronic glomerulonephritis In both instances the evidence of renal damage was known to have antedated the onset of the cutaneous lesions Their conclusion was that a common distinct renal lesion does not exist and that clinically the duration of renal abnormalities is much longer than the pathologic changes found would indicate However, their conclusion is hardly tenable in view of the wide experience indicating the relatively high specificity of the well-developed "wire-loop" glomerular capillary changes

A study was made by Krupp (150) of the urinary sediment in what he terms "visceral angiitis", including cases of periarteritis nodosa and lupus erythematosus Of 21 cases the urinary sediment was normal in three, and in four others of the type that may occur in association with any febrile illness In 14 there was a severe renal lesion and an unusual type of sediment was encountered He compared these observations with the findings in glomerulonephritis and stated that

of his hands He stated that transiently during this period his hands would swell and become deeply reddened for two to three days, following which the skin would become very scaly While the swelling was confined to his hands, the redness extended up the forearms These peculiar episodes occurred about once a week and were brought on by "using the hands in rainy weather" The year before admission his face also became red, swollen, and scaly, particularly after exposure to the sun Subcutaneous nodules were noted about the affected joints

On admission his hands were so swollen that they looked like boxing gloves, and were a brilliant watermelon color This unusual degree of swelling would come and go within a period of a few hours There were hard, non-tender subcutaneous swellings about the large joints These were evanescent Biopsy of the skin showed changes considered to be typical of lupus erythematosus and L E cells were demonstrated

A few weeks prior to death in August, 1952 he was given a new preparation of ACTH, following which his temperature rose, and he became restless and disoriented It was thought that he was having an exacerbation of this illness He soon became gravely ill with high fever disorientation and signs of meningeal irritation A *Cryptococcus* was cultured from the spinal fluid At post-mortem examination, in addition to typical changes of SLE in the spleen, kidneys and the mitral valve, torulosis of the brain and meninges was found

d Renal Manifestations

The occurrence of chronic nephritis in this disease was well recognized by Osler. In 1935, Baehr, Klemperer and Schifrin (5) described conspicuous alterations in the glomerular capillaries The kidneys are usually larger than normal with smooth surfaces sometimes dotted with petechial hemorrhages The most frequent microscopic alteration is an endothelial proliferation in the glomerular capillaries which may be mild or severe, leading to occlusion of the vessel and, if extensive enough, to the development of renal insufficiency. Another lesion of fairly common occurrence is focal necrosis of the capillary tufts, frequently associated with hyaline thrombi. These lesions have been interpreted as an exaggerated or extreme form of the so-called "wire loop" lesion. Allen (2) refers to it as a verrucal capillaritis after the fashion of verrucal endocarditis.

The alteration thought to be pathognomonic is the so-called "wire loop" lesion (Fig. 7) which is present in about 60 per cent of the autopsied cases It consists of an irregularly thickened basement membrane which stains intensely with eosin It may involve only a single capillary loop or there may be a number of such lesions The extent of the lesions varies greatly, and whether or not renal insufficiency develops probably depends on the number of glomeruli involved. Baggenstoss (7) pointed out that the various tubular lesions are not prominent until glomerular changes are advanced when one may observe hydropic vacuolization, fatty change, and hyaline droplet formation in the proximal convoluted tubules Tubular atrophy may be prominent and focal interstitial collections of lymphocytes and plasma cells are seen

In a few of our autopsied cases, the typical lesions of a subacute or chronic diffuse glomerular nephritis have been present with no "wire loop" alterations, and no histological changes of lupus in other organs. In at least one instance the histological picture was that described as intercapillary glomerulonephritis. The absence of the specific lesions of SLE in the kidney or other organs at the time of death does not preclude the diagnosis of SLE as implied by Parelhoff (192).

at post-mortem examination. One patient followed for many months, during which time repeated urine examinations were normal, was found to have numerous histological lesions of SLE in the kidneys The lack of consistent correlation between the clinical and post-mortem findings may explain why patients who are followed for periods, during which they appear to have normal renal function, occasionally rather dramatically develop signs of severe renal damage Thirty-four of the 38 autopsied patients showed some degree of involvement of the kidneys by SLE The following case report portrays the clinical course of a patient who had severe renal disease·

Case 11

M E (#485050) was a 20-year old white female admitted in July, 1950 In 1945 she had an episode of "virus pneumonia", following which she never fully regained her strength In the fall of 1946 she had swelling of the left index finger and several months later developed migratory pain in the elbows, knees and toes with mild swelling In 1947 she was found to have a positive blood STS although there was no familial history of syphilitic infection, the patient denied any sexual contacts, and had had no physical evidence of syphilis She was treated with bismuth and mapharsen intermittently without reversal of her STS She was then well until the spring of 1949 when she developed stiffness of the neck, pain in the right foot, anorexia, and loss of 10 lb in weight She was admitted in September, 1949, at which time she had slight generalized lymph node enlargement, tenderness in her peripheral joints, the fingers showing fusiform swelling, and a positive STS The urine examination disclosed specific gravity 1 020, 2+ albumin, 5 to 10 WBC, loaded with RBC, no casts (menstruating) The hematocrit was 33 and the white cells 6,000 Total serum protein was 6 3, albumin 3 3, and globulin 3 0 gm %

It was thought that she had rheumatoid arthritis By November the joint pains had become more severe and she was more anemic She had generalized lymph node enlargement, and her hands were cold and bluish She was given a transfusion, and started on gold therapy Her urine contained albumin, a few RBC and WBC and a moderate number of casts The treponemal immobilization test was negative, and it was concluded that she had a biologically false positive STS She developed progressive signs of renal insufficiency with azotemia An acneiform eruption appeared on her face and small white ulcers were noted on the gum margins Vascularization was observed about the nail bases

In December, 1949, when she was readmitted for ACTH therapy she was acutely ill, the temperature ranging between 102° and 104° The hematocrit was 33%, sedimentation rate, 38 mm /hr Urinalysis revealed +++ albuminuria, 10–20 red cells and 1–5 granular casts per hpf NPN was 56 mg %, serum globulin, 3 3 gm % Two days after starting on 140 units of ACTH intramuscularly daily the temperature had fallen to within normal limits and she had less joint pain She developed a severe headache and the blood pressure rose from 135/75 to 170/100 mm Hg Although the dose was immediately reduced to 40 units daily, hypertension persisted, she became generally edematous, developed heart failure and the ACTH was discontinued at the end of the third week In spite of a slight reduction in the urinary abnormalities the NPN increased from 56 to 93 mg % during treatment (but fell to 58 mg % one month later) and the PSP excretion, 66% in 2 hours one month before treatment, was 7% two weeks after treatment The hematocrit fell progressively during treatment to 20% Symptoms of active lupus were suppressed during ACTH and for four months thereafter except for a rebound of fever and arthritis for two weeks immediately following treatment

She was readmitted in July, 1950 because of recurrence of anorexia, fever and joint pain of one month's duration The pressure was 140–160/100–110 mm Hg Albuminuria and formed elements in the urine were more plentiful NPN was 120 mg %, PSP excretion, negligible The heart was greatly enlarged and there was a pericardial friction rub For the

the presence in one sample of urine of elements characteristic of all three stages of glomerulonephritis had never been observed in their laboratory. In contrast the urine in the 14 cases of "visceral angiitis" presented in the same specimen red cells, red cell casts, oval fat bodies, fatty and waxy casts and frequently broad casts in addition to abnormal quantities of protein. He felt that such an unusual urinary sediment is a diagnostic aid. These findings were further documented in a subsequent report (171). It was stated that the picture seemed to be characteristic during the acute phase of lupus and to disappear with remission.

Numerous other reports referring to renal lesions in this disease have appeared. Brenner, Leff, and Hochstein (31) described a case of lupus erythematosus without skin lesions in which the clinical picture was that of the nephrotic syndrome with hypertension and with renal insufficiency. Griffith and Vural (91) described the urinary findings in 17 cases and attempted to correlate the abnormalities with pathological data. There was no consistent correlation noted between the clinical and pathological findings. Hypertension was infrequent during the early phases in their cases and when present was associated with advanced renal abnormalities.

Dubois (56) stated that the nephropathy when present is usually of the nephrotic type with the initial appearance of albuminuria accompanied at times by minimal abnormalities in the sediment. Later, there may be a mild increase in blood pressure with the appearance of edema. The non-protein nitrogen and cholesterol in the serum may be elevated. In one of his cases renal manifestations predominated at the onset of the clinical disease.

There was evidence of renal disease in 69 of a group of 105 of our patients. In 41 instances the involvement was mild, slight albuminuria and/or hematuria being present, without significant reduction of renal function. In 24 cases renal disease was considered to be moderate to severe in extent, and 12 patients died in uremia.

Four patients experienced the acute onset of generalized edema, albuminuria, hematuria, and elevation of blood pressure in the period prior to admission, suggesting an episode of acute nephritis. At the time of admission to this hospital, one of these had an entirely normal urine, a PSP excretion of 65 per cent and

albumin and red blood cells in the urine.

There was no evidence of renal disease in 36 patients. Two of these came to autopsy and were found to have normal kidneys. However, it would be wrong to assume that all 36 had no renal involvement due to SLE or to other causes. One of the striking features of this study was the inability to correlate the degree of renal involvement disclosed clinically and the extent of renal damage found at post-mortem examination. Frequently it was noted that patients with little clinical evidence of renal disease had involvement of the kidneys at autopsy. There were instances in which minor changes in the urine and normal renal function tests were associated with extensive structural alterations in the kidneys

which could clearly be attributed to SLE, and it was thought that the changes resulted from the hemolytic anemia and transfusion reactions

Case 13

K B, (#486326) was a 59-year old white female admitted in January, 1949 Her illness began in March, 1947, with "flu" followed by polyarthritis, weakness, and continued fever She subsequently developed subcutaneous nodules, generalized lymph node enlargement, chronic pneumonitis and pericardial effusion Her urine contained a trace to 1+ albumin The sediment was clear The PSP excretion was 50 per cent in two hours While on treatment with ACTH, the NPN rose from 25 to 45 mg % The blood pressure varied between 150/90 and 180/100 mm /Hg Shortly before death in January, 1950 she developed episodes of bloody diarrhea alternating with periods of constipation Her abdomen became greatly distended and she appeared to have a paralytic ileus X-ray showed greatly distended loops of small intestine She also had numerous convulsive seizures At post mortem examination there were scattered "wire loop" lesions of lupus in the kidneys, and a marked arteriosclerotic nephritis The entire intestinal tract was edematous Many of the small vessels showed an arteritis, the mucosa was infiltrated with plasma cells, and there were areas of ulceration There was periarterial fibrosis in the spleen

Case 14

J O (#260256) was a 52 year old white female, admitted in January, 1945, with a history of arthritis and a typical butterfly eruption for 18 months She had a bilateral pleural effusion The white cell count was 3,000 Shortly before death, four months later, she developed generalized convulsions and became aphasic She also had an episode of gross hematuria and the NPN rose to 58 mg % These manifestations were thought to be associated with SLE At autopsy lesions of SLE were found in several organs but the renal manifestations were the result of kidney abscesses due to *E coli*, and a severe ulcerating cystitis She was also found to have a large meningioma, but no vascular lesions of SLE were discovered in the kidneys or brain

e Cardiovascular Manifestations

Although Osler mentioned the occurrence of endocarditis and pericarditis, attention was first focused on the heart with the description in 1924 by Libman and Sacks (160) of a syndrome based on four cases which bore resemblances to rheumatic fever and subacute bacterial endocarditis. The term which they applied to these cardiac changes was "atypical verrucous endocarditis" In 1931 Baehr (4) reported 17 cases of non-rheumatic verrucous endocarditis in which there were striking vascular changes in the kidneys and in other organs Ten of these patients had the butterfly lesions of lupus erythematosus In 1932 Gross (92) described the valvular, endocardial, and myocardial lesions in 11 cases of verrucous endocarditis, seven of which had the dermal lesions of SLE The same author (93) in 1940 analyzed the heart lesions found in the cases of SLE reported by Baehr, Klemperer, and Schifrin Microscopic changes were invariably noted In 17 of 23 cases macroscopic vegetations were described on the valve, the valve pocket, and the mural endocardium Aschoff bodies were absent, as were the valvular endocardial reduplications and palisade formations peculiar to rheumatic fever There was a marked tendency to valvular necrosis There were frequent vascular lesions in the pericardium and myocardium of a type rarely observed in rheumatic fever Vascular lesions were not confined to the heart, but were found in other organs particularly the vessels of the kidney

first time she complained of severe difficulty in swallowing and x-ray showed changes thought to be compatible with scleroderma of the eosphagus Because of high fever and [illegible]

examination revealed the kidneys to have extensive alterations due to lupus There were patches of organized pneumonia There was pericardial thickening and focal myocardial scarring Her esophageal ulcers were secondary to arteriolar lesions produced by lupus

Of the 38 patients who came to autopsy, SLE alone was responsible for varying degrees of renal damage in 26. In the remainder, the principal lesions were considered to be due to infection, lower nephron nephrosis or arteriosclerosis, the changes of SLE either being minor or absent

It has been said that patients with SLE seldom develop an appreciable degree of hypertension during the course of the illness. Eleven of the 34 cases reported by Shearn and Pirofsky (234) had elevation of systemic blood pressure In five it was in association with severe renal involvement, in one related to toxemia of pregnancy, and in another developed during cortisone therapy but persisted after its discontinuation In our own series, 15 patients had blood pressures greater than 140/90. Eight of these had hypertension associated with azotemia, and in several of this group the hypertension did not appear until the onset of nitrogen retention In four of these 15 patients there was evidence of a severe degree of arteriosclerosis in addition to the SLE One was recovering from a recent episode of an acute glomerulonephritis following a streptococcal infection, and another developed hypertension while on cortisone. A final patient had mild hypertension in association with uncomplicated SLE Therefore, in this group, with but one exception, significant elevation of the blood pressure occurred only when renal involvement was so extensive that nitrogen retention had occurred, or when other factors, such as arteriosclerotic degeneration or infection, were associated with lupus Five other patients who had varying degrees of renal lupus at post-mortem examination and who died in uremia had no elevation of blood pressure

In only one patient given cortisone were the renal lesions which have been produced in animals by this hormone observed (216) These changes were minimal Several patients who were given ACTH and/or cortisone for protracted periods of time showed no significant evidence of renal involvement at post-mortem examination

While renal injury is common during the course of SLE, it is a serious error to assume that SLE is the cause of all manifestations of renal disease which occur. It must be emphasized that other causes, particularly infection, play a significant role in damaging the kidneys either alone or in association with the underlying disease The following brief case reports illustrate this point:

Case 12

[illegible] had albumin,



FIG 9 Valvular and myocardial lesions in a patient who died with SLE A There are fibrinous vegetations attached at the angle of union of the mitral valve with the myocardium This is a typical location for these lesions in SLE in contrast to rheumatic fever B Swollen collagen fibers with small round cell exudate are present in the myocardium Such lesions lack the large mononuclear cells of typical Aschoff bodies

On the other hand, Rich (214) believed that the focal myocardial interstitial collagen degenerations may be only quantitatively different in SLE and rheumatic fever He showed the morphological identity of many of these myocardial collagen degenerations in SLE and rheumatic fever as well as in cases of periarteritis nodosa, and anaphylactic hypersensitivity both in man and in animals

In the autopsies in our series it has been noted that the valvular endocarditis is apt to be on the under surface of the mitral valve, often at the base, in contrast to the usual location of the vegetations in rheumatic fever on the outer surface of the valve

There may be striking clinical findings referable to the cardiovascular system at various stages in the disease Systolic murmurs are not uncommonly found as noted by Shearn and Pirofsky (234) but when the patient has fever and anemia their significance is difficult to evaluate. Four of their patients also had a diastolic apical murmur In two of these, endocarditis of the mitral valve was found at post-mortem examination In another with a presystolic rumble small vegetations were present on the auricular surface of the mitral valve near the free margin and the chordae tendinae were thickened In 14 of their patients symptoms and

Baggenstoss (7) described the frequent occurrence of diffuse or focal fibrinous pericarditis If healing had occurred the pericardial sac was obliterated by fibrous adhesions The exudate contained polymorphonuclear cells, and organization by fibroblasts appeared early He stated that the only distinctive lesion was the so-called "fibrinoid degeneration of the interstitial ground substance and collagen fibers". The ground substance became deeply eosinophilic, and there was irregular thickening of the collagen fibers which were highly refractile and intensely eosinophilic (*Fig 8*). *Typical* verrucous endocarditis was noted in 40 per cent of the cases studied by this author. Such lesions appeared as dry, granular vegetations up to 3 to 4 mm in size which were single or conglomerate. On microscopic examination there was an intense valvulitis characterized by fibrinoid degeneration of collagen which protruded on the surface becoming visible as a vegetation. *There was an accompanying necrosis of tissue and an exudative reaction which* was usually more severe than one observes in rheumatic valvulitis (Fig 9A) These changes led to the development of granular basophilic masses consisting of nuclear debris along with basophilic fragments of cytoplasm, the so-called "hemotoxylin body". In the myocardium similar lesions characterized by fibrinoid degeneration of interstitial collagen fibers associated with an exudative reaction were described (Fig. 9B). These lesions were thought to be different from those in rheumatic fever where proliferative phenomena are predominant.

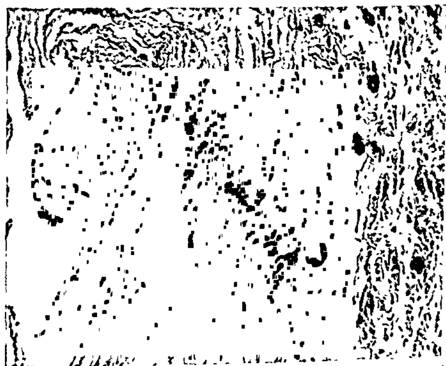


FIG 8 This illustration shows a focal area of collagen swelling and degeneration in the epicardium of a patient who died with SLE

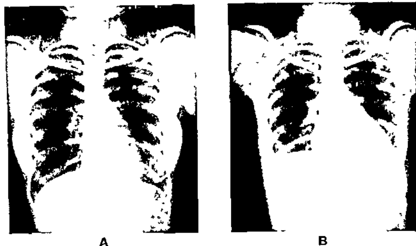


FIG 11 Teleoroentgenogram of the chest in a patient who died and was found to have extensive myocarditis due to SLE A Several months before the development of cardiac manifestations B After admission to the hospital because of cardiac insufficiency

times they were scattered and focal The intimal lining of the small coronary vessels was sometimes involved with occlusion and resultant anemic necrosis These vascular lesions were entirely similar to those seen as a consequence of rheumatic fever At other times the heart muscle fibers were atrophic or replaced by patches of connective tissue or infiltrated with cells Less than half of the patients with lupus myocarditis had manifestations of cardiac insufficiency In the remainder, cardiac function was not overtly affected by the myocarditis In this group of patients, there were two who were not considered to have disease of the myocardium on clinical grounds and who were given ACTH without restriction of salt in one instance, and when renal function was depressed in the other Both patients rapidly developed heart failure and at post-mortem examination extensive lupus myocarditis was discovered Thus, an individual may have a significant amount of myocardial disease with little or no clinical evidence of its presence It is, therefore, important to avoid stress on the cardiovascular system during the active phase of this disease Following an acute episode of lupus, a period of time should be afforded for myocardial healing to occur The analogy to the clinical course of rheumatic fever is apparent

The clinical course in two patients thought to have myocarditis and SLE is described in the following case reports

Case 19

This 31-year old colored female (I V #614097) entered complaining of dyspnea In May, 1952 she developed a sore throat followed in three weeks by migratory polyarthritis In June, 1952 polyarthritis reappeared with fever and one month later substernal pain and pain in the left lower chest which was at first pleuritic in type The symptoms gradually subsided In August, 1952 an L E cell test was positive She had no fever, but there was

In two instances, at post-mortem examination, an unsuspected purulent pericarditis was found which contributed to the death of the patient. The following case report presents the findings in one of these patients:

Case 16

I C (A-47972) was a 13-year old Negro female admitted in March, 1948 She had had SLE for three years Terminally, she developed high fever, and there were signs of a large effusion in the pericardium, and also in the pleural spaces These were considered to be due to SLE At autopsy, however, in addition to lupus it was found that she had had a staphylococcal septicemia with multiple abscesses in the heart muscle and a purulent pericarditis

In one-third of the patients in our series who came to autopsy, the verrucous bacterial vegetations described by Libman and Sacks were found. They were present predominantly on the mitral valve but the other valves were occasionally implicated The presence of the endocarditis usually had no effect on the heart or circulation Generally, the only manifestation was a soft apical systolic murmur. A similar type of murmur was frequently heard in patients who came to post-mortem examination and had no valvular abnormality In two patients, signs of mitral stenosis were noted during life although at autopsy the only abnormality of the mitral valve was Libman-Sack's endocarditis·

Case 17

A V (#445357) was a 40-year old white male who died in January, 1949, seven years after the apparent onset of SLE On the initial examination the first mitral sound was described as loud and snapping A systolic and a crescendo pre systolic murmur were noted at the mitral area X ray of the heart showed prominence of the pulmonary conus and EKG revealed right axis deviation It was considered that he might have both rheumatic heart disease and SLE, but at post-mortem examination only the lesions of Libman-Sacks were seen on the mitral valve

In two cases there was a superimposed infection, in one instance on the tricuspid and in the other on the aortic valve:

Case 18

heard It was thought that he had acute bacterial endocarditis superimposed upon an aortic valve which had been implicated by the lupus process He was successfully treated with massive dosages of aureomycin and penicillin Since that episode he has had persistent mild congestive *heart failure*

Of the autopsied patients, 55 per cent had some form of myocardial involvement and in 80 per cent of these the myocardial changes were considered to be due entirely to SLE (Fig 11). In three instances, myocardial damage was thought to be the result of coronary arteriosclerosis and hypertension; and in a single incidence, myocardial failure was the result of multiple abscesses in the myocardium secondary to staphylococcal sepsis At times the alterations produced in the myocardium by the lupus process were very extensive, at other

Taylor (205) the persistent pulmonary consolidation was the most prominent part of the patient's illness, being noted for a period of over eight months Foldes (71) described a chronic interstitial pneumonitis which leads to atelectasis and may cause respiratory failure Baggenstoss (7) noted this type of pneumonitis, and in addition observed a peculiar basophilic mucinous edema of the alveolar walls and the peribronchial and perivascular tissues in association with an interstitial pneumonitis and alveolar hemorrhages He stated that these lesions are distinct from the ordinary pyogenic bronchial pneumonia, with or without organization, which so frequently complicates the terminal stages of SLE In this "atelectasizing" pneumonitis the alveolar walls and peribronchial and perivascular connective tissues are apparently the primary sites of an inflammatory process obliterating the alveolar spaces

Even with the recent expansion in our knowledge of this disease picture the frequency with which pulmonary manifestations occur has not been generally noted Dubois (56) refers to the presence of pleurisy and pleural effusion in 55 per cent of his series but makes no mention of intrinsic pulmonary involvement Israel (124) stated that pulmonary involvement is common but that specific lesions such as disseminated perivascular changes, chronic interstitial pneumonia and massive pleural effusion are relatively infrequent He recognized the frequency with which bacterial pneumonia complicates the disease Since pulmonary manifestations occasionally dominate the clinical picture he advised search for L E cells in patients with recurrent pneumonia, and infiltrations or pleurisies of unknown cause

These various types of intrinsic pulmonary involvement were observed in 46 of 105 patients in our own study Twenty patients had pulmonary changes considered to be produced by SLE, six had pulmonary tuberculosis, five lobar pneumonia, two lung abscesses, nine lobular pneumonia, two aspiration pneumonia and one repeated hemoptyses

✓Seven of the twenty patients suspected of having "lupus pneumonitis" came to autopsy and were found to have characteristic findings These consisted of hyaline membranes in the alveoli, focal necrosis of alveolar walls with capillary thrombi, areas of organizing interstitial pneumonia and hemorrhage, and metaplasia of the bronchiolar epithelium These are changes which are similar to those seen in rheumatic pneumonitis, periarteritis nodosa, "anaphylactic" pneumonitis due to sulfonamide allergy as well as in serum sickness (213) The nature of these pathologic alterations is such as to produce focal atelectasis and, if extensive, there may be interference with the transport of oxygen across the alveolar membrane, resulting in cyanosis and dyspnea (Fig 12)

The clinical manifestations in these patients with proven "lupus pneumonitis" were varied *In several instances as illustrated by the following two cases reports* the lungs were extensively involved and respiratory manifestations became predominant as the illness advanced

Case 21

R S (#561950), a 64 year old white male, was admitted in January, 1951 complaining of fatigue for six to eight months Generalized soreness of his muscles and joints associated with anorexia, nausea, and persistent diarrhea, began five months prior to admission He

[illegible]

four weeks She then noted dyspnea but digitalization and salt restriction resulted in no improvement Her dyspnea was progressive and she developed orthopnea and edema of the ankles The blood pressure was 95/70, and numerous rales were heard at both lung bases The left border of cardiac dullness was in the anterior axillary line The sounds were of poor quality, and a gallop rhythm was heard Electrocardiogram revealed inverted T waves compatible with the diagnosis of myocarditis Treatment was instituted with cortisone Her pressure remained low, and the gallop rhythm persisted for a few days but then rapidly improved

Case 20

This 34-year old colored female (E M #639062) was admitted in May, 1953 complaining of polyarthritis In 1940 she was told that she had "bad blood" but her spinal fluid was normal During 1951 she developed recurrent stiffness and pain in the hands In January, 1953 a diagnosis of rheumatoid arthritis was made and she was placed on cortisone She became dyspneic and in February developed chills, fever, and malaise One month before admission she was digitalized Physical examination on admission showed temperature 101 8° F , pulse 124, respirations 36, blood pressure 100/60 The precordium was active with visible pulsations at the apex and base The heart was enlarged, the rate was rapid and there was a gallop rhythm There was hepatomegaly The L E cell test was positive Biopsy of a lymph node showed massive caseous necrosis with calcification probably due to tuberculosis X-ray of the chest showed enlargement of the left cardiac border with prominence of the hilar vessels There were many well localized calcified densities throughout the upper chest and in the axillae as well as in the neck, thought to be calcified lymph nodes Electrocardiogram revealed abnormally low T waves and right axis deviation Vital capacity was reduced as was the maximum breathing capacity She was thought to have disseminated tuberculosis, possibly precipitated by the previous cortisone therapy, and antibiotic treatment

[illegible]

and nydrazid There was remarkable improvement with defervescence Her heart became smaller in size and the gallop rhythm disappeared She developed bradycardia The cortisone dosage was lowered to 150 mg , then to 100 mg She was discharged much improved after five weeks The T waves in all three leads returned to a normal appearance, and there was a change from right axis to slight left axis deviation

Abnormalities in conduction were present in six patients. In two there was auricular fibrillation; in three, first degree heart block, and in one, a right bundle branch block The latter, however, was considered to be congenital and not due to lupus

f Pulmonary Manifestations

It is well recognized that pleural involvement is one of the hallmarks of SLE, but less generally appreciated that intrinsic pulmonary involvement is frequently present The clinical signs are usually those of a chronic pulmonary consolidation which must be differentiated from complicating pulmonary infections or lung involvement due to other causes Osler recognized that pulmonary lesions may occur. Later, Tremaine (255) reported a case with long-standing consolidation of the lung thought now to be due to lupus. In the case reported by Rakov and

gressed and she died Autopsy revealed typical changes of lupus scattered diffusely throughout both lungs There was also a mild interstitial myocarditis

These two patients illustrate some of the clinical features of extensive involvement of the lungs by SLE. Respiratory symptoms were prominent throughout their course, which was marked by the development of progressive tachypnea, dyspnea, and cyanosis, unrelieved by the administration of oxygen. The physical alterations were never very pronounced, scattered fine or course râles being the only evidence of pulmonary involvement X-rays showed only non-specific fibrotic changes. It is of interest that while ACTH had a beneficial effect in reducing the fever and the joint and skin manifestations of lupus, the pulmonary alterations were little affected. The clinical course of these patients was suggestive of that noted in patients with "peculiar pneumonia" described by Tumulty, Berthrong, and Harvey (257) although the morphological changes were at least quantitatively different

In contrast to these patients are two in whom autopsy disclosed spotty lupus involvement of the lungs which was unsuspected during life Physical examination of the lungs failed to show significant changes In one instance, the x-ray also was reported as clear but in the other, extensive "non-tuberculous" infiltration was described The physical evidences of "lupus pneumonia" may be minimal and extensive involvement remains undetected unless serial x-rays are taken. A chronic pneumonitis was not uncommon in our experience as illustrated by patients who had persistent signs of pulmonary involvement for fully six months

In addition to this group in whom pulmonary lesions were demonstrated histologically, 13 patients were considered on clinical grounds to have this specific type of pulmonary involvement Five are of particular interest because the pulmonary changes were evident for many months The cough was usually hacking and dry but was occasionally productive There were only scattered fine and coarse râles heard Outspoken signs such as dullness and change in the character of the breath sounds were unusual The observed physical and roentgenographic changes were usually located in the basilar portions of the lung fields

In reviewing the clinical course of these patients, we are impressed by the frequency with which elevation and fixation of one or both diaphragms were observed, with areas of plate-like atelectasis above (Fig 13) In such areas one may hear showers of course and sticky râles Since these patients are still alive, it is impossible to be certain that these pulmonary changes were due to lupus, but the inability to isolate any pathogenic organism from the sputum or blood, and repeated failure to alter the changes through the administration of one or several antibiotics, makes lupus the likely cause These episodes of "lupus pneumonitis" may occur at the beginning of the disease, or anytime thereafter They not infrequently recur

In addition to the group of patients who were believed to have had a chronic "lupus pneumonitis", eight patients had an acute episode of pneumonitis The clinical characteristics of these acute episodes were the same as in the chronic form described above

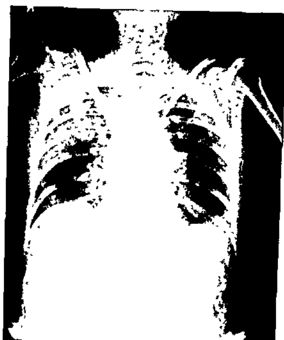


FIG 12 Roentgenogram of the chest in a patient who died with SLE and was found to have extensive "lupus pneumonitis". During life there were manifestations of severe pulmonary insufficiency

became extremely weak and feverish Shortly before admission he developed a non-productive cough A mass was found in the right kidney At operation this proved to be a benign cyst Post-operatively his condition grew worse He developed persistent tachycardia and acceleration of the respiratory rate, despite the use of oxygen A pleural friction rub was heard over the right anterior chest The temperature varied between 101° and 103°. The L E cell test was positive On the thirteenth post-operative day, ACTH was started in a dosage of 50 mg intravenously daily The temperature became normal, and the pulse and respiratory rate decreased When, however, the ACTH dosage was reduced, the fever returned and the respiratory distress became more marked Administration of penicillin and streptomycin failed to alter the course Tachypnea and tachycardia became excessive, and he died with severe pulmonary insufficiency At post-mortem examination there were extensive changes of lupus throughout both lung fields, with hyaline membranes lining the alveoli, areas of organized pneumonia and hemorrhage, and metaplasia *of the bronchial* epithelium

Case 22

E S (#537561) was a 62 year old white female who in 1939 had an illness characterized by fever and arthralgia following which malaise persisted In December, 1949 she developed polyarthritis which became progressively worse She was found to have fever, anemia, leucopenia and hematuria In February, 1950 she developed an erythematous eruption of the butterfly area On admission in May, 1950 she was critically ill with dyspnea, cyanosis, and tachycardia With ACTH administration her temperature fell to normal, the joint manifestations subsided, and the erythema faded However, she continued to have tachycardia, dyspnea, and cyanosis, and there were persistent signs of pneumonitis in both lower lung fields X-ray showed diffuse infiltration at both bases Her respiratory distress pro

gressed and she died Autopsy revealed typical changes of lupus scattered diffusely throughout both lungs There was also a mild interstitial myocarditis

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form described above



FIG 13 Roentgenogram of the chest in a patient with SLE who had clinical evidence of moderately severe pulmonary involvement Note the elevation of the diaphragm and the plate-like areas of atelectasis A Antero-posterior view in full inspiration B. Lateral view

Three patients gave a history of "virus pneumonia" which preceded by a number of weeks or even longer other manifestations of SLE These episodes were characterized by a protracted course, dearth of physical signs, failure to respond to antibiotics and a continuation of fever and malaise until the development of other abnormalities made the diagnosis clear.

It is important to note that bacterial infections of the lungs were common during the course of SLE and may be confused with true "lupus pneumonitis". Thus, in this group of 46 patients, six had pulmonary tuberculosis, one with an associated tuberculous empyema, five had pneumococcal lobar pneumonia, nine had lobular pneumonia due to a variety of organisms, two succumbed from aspiration pneumonia and two had a lung abscess. It is often difficult to determine on clinical grounds alone whether one is dealing with pneumonitis due to lupus or to some bacterial infection The error may be made of assuming that a *particular pulmonary manifestation is due to lupus when a bacterial agent is responsible* The therapeutic implications of such an error are obvious, as is illustrated by the following cases:

Case 23

L D (#532508) was a 19 year old Negro female admitted in March, 1950 A month before she developed "black spots" on her face followed by the insidious onset of malaise, polyarthralgia, anorexia, pain in the chest, and cough Her tongue and face became swollen On admission her temperature was 104° and there was extensive angioneurotic edema L E cells were found in the peripheral blood, and she was started on cortisone with improvement

and had a generalized convulsion She was readmitted in July and given penicillin and

cortisone with some improvement One week before the final admission in September, 1950 pain began in the right chest and her cough became severe She became oliguric and the NPN rose progressively Cortisone was given but halted when convulsive seizures returned Basilar rales were heard and x-rays showed an infiltrative process at the right base She was considered to have "lupus pneumonia" There was no response to therapy with penicillin At postmortem examination there was a large abscess cavity in the posterior segment of the right lower lobe communicating with the bronchus, surrounded by a large area of consolidation *Pseudomonas* was cultured from the heart blood and the lung abscess It was clear that the patient had had a septicemia with focal areas of necrosis scattered in the spleen, brain, kidneys, and liver It was thought that the lung abscess might have been the result of an acute arteritis due to lupus, with secondary infection, although she may have aspirated foreign material during a convulsion In addition there were periarterial fibrosis in the spleen, "wire loop" lesions in the kidneys and abacterial vegetations on the mitral valve

Case 24

P M (#569753), a 41 year old white female, for eight years had transient episodes of arthralgia, for two years a recurrent facial eruption, and for six months typical butterfly rash On admission in April, 1951 she was in uremia Shortly after entry she had a shaking chill, signs of pneumonitis developed at the left base, and there was elevation of the temperature She was treated with penicillin with subsidence of symptoms and signs, but shortly after the penicillin was discontinued she again had a chill, signs of pneumonitis and pneumococci were found in the blood Once more she responded to penicillin but only temporarily She grew rapidly worse and thirty five days before death she was begun on 25 mg of cortisone daily which was gradually increased to 100 mg At postmortem examination a totally unsuspected miliary tuberculosis was found, as well as lesions typical of SLE

Involvement of the pleura is common during the course of SLE Sixty patients in our series had one episode of pleurisy and fourteen had repeated attacks The pleurisy was usually dry but at times was associated with a small to moderate effusion The effusion was never massive unless there was some complicating infection such as tuberculosis The episodes of pleurisy occurred at various periods during the illness, at times being one of the earliest manifestations Pneumonitis was almost always associated with pleural involvement In addition to typical pleurisy, a number of patients complained of vague aching pains in the chest, although no objective signs were present Episodes of pleural pain at times persisted for several weeks and were very distressing

g Gastrointestinal Manifestations

In Osler's cases gastrointestinal manifestations were prominent Certain authors have suggested that his were not cases of SLE because later reports had not confirmed the frequent occurrence of gastrointestinal symptoms in this disease However, with increasing experience it has become clear that the gastrointestinal tract is frequently the site of typical vascular lesions with associated clinical symptoms In various reports the manifestations noted have included anorexia, nausea, vomiting, diarrhea and abdominal pain severe enough to simulate an acute surgical condition of the abdomen Dysphagia has also been reported (6) Various authors have attributed the abdominal pains to peritoneal serositis or involvement of the retroperitoneal connective tissues Reifenstein and his associates (210) found evidence of peritonitis in 72 per cent of their

autopsied series with perihepatitis and enlargement of the liver in one-third. *Pancreatitis* was also noted. Dubois (56) stated that gastrointestinal symptoms were prominent in 40 per cent of his cases In one instance the initial symptoms were referable to this system and gastrointestinal difficulties represented the chief complaint in almost 10 per cent. The abnormalities were due to vascular involvement in the bowel wall with infarction or hemorrhage. Most of the patients had abdominal pain which was constant or cramping, associated with vomiting and with diffuse abdominal tenderness Occasionally, diarrhea, sometimes bloody, was noted.

In our cases manifestations indicating involvement of the gastrointestinal tract were not uncommon Seven patients had anatomical lesions of the esophagus. Three complained of epigastric burning and at postmortem examination an extensive diphtheritic esophagitis was found in all Four had ulceration of the esophagus in association with collagen degeneration and arteritis of the characteristic type seen in lupus. The findings in one of these patients are of particular interest: (Case 11) (Fig. 14A)

Seven patients complained of abdominal cramps associated in four with hemorrhage from the bowel In three an acute arteritis with thrombosis of small vessels had resulted in ulceration of the small intestine In one the bleeding was in association with obstructive jaundice and in another with hemorrhage secondary to thrombocytopenia. Two of these patients deserve special mention. (Case 13) (Fig 14B).


A


B

[illegible] Roentgenogram after barium swallow in a patient with SLE who complained [illegible]

greatly distended loops of small intestine At autopsy [illegible] testine showed an arteritis and there were areas of ulceration

Case 25

S R (#561950) was a 64 year old white male who was admitted in January, 1951 Eight months prior to admission he began to have malaise and musculoskeletal aching Shortly thereafter he developed anorexia with nausea and persistent diarrhea A few weeks prior to death in March, 1951 he began to have frequent bloody stools and required repeated transfusions He also had severe epigastric distress At postmortem examination there was extensive arteritis with thrombosis of the vessels of the small intestine resulting in multiple ulcerations There was also a diphtheritic esophagitis, and extensive lupus pneumonitis

The large bowel was involved in five cases and abdominal pain and diarrhea were prominent clinical manifestations In four of these there was arteritis with ulceration of the mucosa Ileocecal tuberculosis accounted for the symptoms in one Another patient had persistent diarrhea and bloody stools, but no postmortem examination was performed

h The Liver, Spleen, and Pancreas

Hepatomegaly occurs in patients with SLE, but it is not an outstanding feature and jaundice is unusual Griffith and Vural (91) noted hepatomegaly in six of 18 cases Pathological findings in the liver of these 18 patients were slight to moderate with fatty degeneration in six, some necrosis of liver cells in one, and in the remainder no significant alterations Dubois (56) showed an illustration of an arteritic lesion in the liver in a nine year old girl with classical SLE Hepatomegaly was found in 34 per cent of his cases This author noted that vessels in the pancreas may be involved and he cited one patient who developed epigastric pain radiating to the back, associated with vomiting, and a serum amylase level was 2400 units In addition to lesions characteristic of SLE autopsy revealed acute pancreatitis secondary to disease of small arterioles

The earliest reference to periarterial fibrosis in the spleen is that of Libman and Sacks (160) Shaumann and Introzzi (233) in 1931 described this change in three cases Klemperer, Pollack and Baehr (146) in their report of 19 cases of SLE first called attention to the frequency with which this lesion is noted Kaiser (134) studied 18 cases, and in most the spleen was definitely, but not markedly, enlarged Periarterial fibrosis was found in 15. It was noted as present "when the periarterial collagen of the penicilliary or follicular arteries, which normally is closely packed and without evidence of hyalinization, was found to be present in at least three layers, around at least half the circumference of the vessels, producing the appearance of concentric rings" (Fig 15) In a control study, including 970 consecutive autopsies, some degree of periarterial fibrosis was found in 22 cases, an incidence of 2 3 per cent In no instance, however, was it as extensive either in size or in distribution as in SLE

The reported incidence of splenomegaly in SLE has varied considerably Coburn and Moore (43) noted it in seven of 30 cases Jessar and his co-workers (129) reported enlargement of the spleen in 17 per cent of 168 patients Dubois (56) stated that the frequency of splenomegaly has been over-emphasized, having been noted in only 8 1 per cent of his cases He stated that it is usually present in association with hepatomegaly when there is an hemolytic anemia

In one other instance, in which there was striking lymphadenopathy, a diagnosis of reticulum cell sarcoma was made on the basis of a biopsy. The lymph nodes and the spleen decreased in size after administration of nitrogen mustard This patient was later proven at autopsy to have SLE.

3 Nervous System Manifestations

Only recently has the frequency of nervous system involvement been recognized Daly (48) noted the common occurrence of a "toxic delirium" manifested by confusion, disorientation, restlessness and irritability. In the terminal stages, coma frequently supervened. A psychotic picture with delusions and hallucinations sometimes developed. He also observed convulsions in a number of patients who were not azotemic He stated that in the experience of others, neurologic examination may be entirely normal or disclose scattered findings indicating involvement of the motor system, such as hyperreflexia, clonus, and a positive toe sign Examination of the spinal fluid showed some increase in protein content in 10 to 15 per cent of the reported cases.

Further evidence of the frequency of nervous system abnormalities was presented in the analysis of the first 32 cases of the present series (258). In the previous year Sedgwick and Von Hagen (230) had described cases of SLE and periarteritis nodosa with neurological manifestations In Jessar's series (129) convulsions were present in 9 per cent, toxic psychosis in 5 per cent, and hemiplegia in 2 per cent Neuronitis, focal central nervous system lesions, cerebral hemorrhage and chorea were seen in isolated instances

Dubois (56) noted that *multiple central nervous system manifestations may* occur due to cerebral angiitis He presented illustrations demonstrating vascular changes in a spinal cord arteriole and periphlebitis in the floor of the third ventricle of a patient who had convulsions and mental deterioration during the course of SLE Thirty-five per cent of his cases had seizures of which 30 per cent were attributed to the disease and 5 per cent to treatment. He stated that seizures are most common in the terminal phase of the illness. In his experience *another common terminal event, as was previously* pointed out by Tumulty and Harvey, was the occurrence of hemiplegia due to lupus vasculitis This author has also seen one case of severe polyneuritis, apparently due to nutrient artery involvement, similar to that described by Heptinstall and Sowry (118) Dubois noted signs of meningismus with a pleocytosis of several hundred leucocytes, either lymphocytes or polymorphonuclear leucocytes, along with increased protein in four cases In his series organic psychoses of various types occurred in 29 per cent.

Piper (198) reported one case in which vascular involvement of the spinal cord produced an infarct with resultant paralysis of the lower extremities

Russell, Haserick and Zucker (224) analyzed a series of 144 patients with SLE, 15 per cent of whom were reported to have had convulsions. Fifteen had seizures only during the terminal phase. Four had isolated grand mal seizures during the active preterminal phase They report on 28 patients with positive L. E. cell tests, seven of whom had convulsions In two instances the diagnosis

of idiopathic epilepsy had been made years previous to the onset of recognized SLE Other neurological manifestations such as manic behavior, mental confusion, neurogenic bladder dysfunction, amaurosis and paraplegia were noted terminally in the three patients Two types of electroencephalographic alterations were described· 1) records characterized by moderately high voltage activity at a rate of 3 to 7 cycles per second with delta waves which frequently exhibited disparity between the two sides, and, 2) abnormal records of medium voltage activity having a rate of 6 to 8 cycles per second and showing a diffuse pattern often interspersed with long or short runs of normal alpha activity

Glaser (79) recently reviewed the central nervous system manifestations in SLE. The vascular lesions had a predilection for the gray matter of the cerebral cortex, particularly the presulcal areas, which may explain the frequent occurrence of convulsive seizures The parenchymatous changes, consisting of focal or disseminated encephalomalacia often with hemorrhage or cyst formation, were secondary to the involved vascular supply

More than one-third (37 per cent) of the cases in our series developed some abnormality of the nervous system Eighteen had convulsive seizures In three instances these were associated with hemiplegia and in one with motor aphasia Four individuals had a toxic psychosis in addition to convulsions Two of the patients with convulsions had repeated attacks over a period of several years. Twenty had one or more acute psychotic episodes In four these were associated with convulsive seizures and in two with a transient bilateral ptosis Other instances of abnormal nervous function included two patients with hemiplegia, one with potassium intoxication during uremia due to SLE, and another with manifestations simulating myasthenia gravis One patient died of a complicating *Torula* meningitis

Neurological dysfunction almost invariably developed during a very active phase of the disease Only two of the 40 patients had nervous system lesions during a chronic or subacute phase, both had repeated epileptic seizures Since these nervous system alterations were so commonly associated with an exacerbation of the disease, they are ominous signs

In 12 of the 18 individuals who had convulsive seizures during the course of their illness, SLE alone was considered responsible In two instances there was hypertension and azotemia and at postmortem examination, there was involvement of the kidneys by SLE In case 14, already described, there was a dural meningioma in the left parietal area In another patient the seizures occurred during the terminal phase of lupus, complicated by streptococcal septicemia and uremia In another, in addition to a mild elevation of the non-protein nitrogen, the illness was complicated by an hemorrhagic tendency

In 14 of the patients who had psychotic episodes, SLE was the only demonstrable cause In three instances the psychosis appeared when the patient had an intercurrent infection, and in two others the course was complicated by hypertension and azotemia In another hepatic disease may have played a part

Of the 40 patients manifesting disordered brain function, 31 either were never given ACTH or cortisone or had their nervous system manifestations prior to

receiving them In three instances in which nervous system abnormalities occurred while ACTH or cortisone was being given, the reaction developed when the dose had been reduced with a subsequent exacerbation of the lupus process Convulsions and a psychotic reaction occurred in five cases following an allergic reaction to ACTH, and in each instance were associated with other indications of an exacerbation of the SLE.

As mentioned above, three patients had transient bilateral ptosis during their illness The course of one is of unusual interest:

Case 27

R S. (#160926), a 17 year old white female, was admitted in September, 1952 with the story that 18 years previously she began to feel exhausted She lost her appetite, frequently felt nauseated and had recurrent headaches She developed a low-grade fever The following year she noted diplopia and ptosis of the left lid A diagnosis of myasthenia gravis was made The spleen was palpable, and she had 5 per cent eosinophils She was given neostigmine with equivocal improvement She returned in a few months stating that her symptoms had vanished, and she no longer needed neostigmine In 1936 she developed a typical eruption of lupus erythematosus on her face and ears In 1940 she developed polyarthralgia which lasted for many years Early in 1952 she had an exacerbation of the migratory polyarthritis and a low grade fever On the day of admission she developed a pleuritic pain in the left chest A doubtful STS was recorded There was no history of syphilis and the treponemal immobilization test was negative The L E cell test was positive

In reviewing the course of this patient's illness, it seems reasonable to conclude that the neurological manifestations which she had fully 17 years prior to admission were due to SLE and not to myasthenia gravis.

The two other patients who developed neurological changes during a chronic state of SLE should be briefly mentioned In one of these also, the initial episode in the illness was neurological in nature:

Case 28

[illegible] 1918

[illegible]

examination except questionable ptosis of the left lid It was thought that she might have had a mild cerebral vascular accident, but it seemed most likely that this was an hysterical [illegible] treatment with [illegible] she had a [illegible] biological [illegible] al blood It [illegible] 0, and that

SLE was responsible

Case 29

G M (#606719), a 24 year old white female, was admitted in May, 1952 because of convulsive seizures which she had had since childhood When she was eight years of age she was struck on the head with a golf club Shortly thereafter she began to have "peculiar absences" which were interpreted as petit mal attacks At 16 years she had her first grand mal attack and these occurred at irregular intervals thereafter When she was 19 years of age her knees became swollen, hot and tender and after that time she had almost constant migratory joint pains Four years prior to admission, she developed an eruption on her

legs and buttocks In 1949 the blood STS was positive, although there was no history to suggest syphilis On admission she had an erythematous eruption on her legs and buttocks Her fingers showed the fusiform changes seen in rheumatoid arthritis The blood STS was negative The spinal fluid was normal EEG showed a focus with high spikes in the right temporal region L.E. cells were found

It is possible that this patient's epileptic seizures may have been due to cerebral damage caused by SLE although other causes cannot be excluded

While abnormalities of the brain frequently occur during the course of SLE, nervous system involvement may have some other basis as illustrated by Cases 10 and 14

Lumbar punctures were performed in 30 of our patients In eight without specific nervous system abnormalities (six were acutely ill with high fever), the spinal fluid findings were normal in all but one who had an initial pressure of 200 mm.³ CSF, 18 mononuclear cells per mm.³ and a protein concentration of 61 mg %. In the 22 with signs of nervous system dysfunction at the time of puncture (14 had convulsions), the results were abnormal in ten

The protein concentration was elevated (above 50 mg per cent) in seven of these ten cases during seizures or coma (one case) Three of the seven and one other had abnormal colloidal mastic curves In one patient who had had convulsions the protein was 930 mg per cent, and the mastic curve 1245555432 In another case, the protein concentration was 128 mg per cent after a series of seizures, and 25 mg per cent after ten days Four months later, following a second series of convulsions the protein was 70 mg per cent In another case the protein was 93 mg per cent when no neurological manifestations were present, and on another occasion 86 mg per cent following several convulsive episodes

A pleocytosis, predominantly polymorphonuclear, was demonstrated in the spinal fluid of each of three cases (250, 350 and 550 WBC per mm.³) One was case 10 with cryptococcal meningitis The other two had a concomitant leucocytosis in the peripheral blood, but an infectious agent was not uncovered in either case

i. Retinal Lesions

In 1935 Pillat (197) described the funduscopic changes in 48 cases of chronic lupus, in 16 of which he found isolated changes resembling healed tuberculous choroiditis As early as 1929 Bergmeister (22) had reported lesions which he thought were metastatic tubercles in the retina in a patient with SLE in whom necropsy disclosed disseminated tuberculosis The eyes were not examined histologically, but from the description it seems likely that these were cotton-wool exudates or cytoid bodies In the cases reported by Baehr, Klemperer, and Schifrin (5), 12 of 23 had fluffy exudates in the fundi with perivascular hemorrhages as well as circumpapillary edema in two cases Kurz (154) in 1938 was probably the first to consider that these white patches consist of gangliaform degeneration of nerve fibers (so-called cytoid bodies) He thought that the lesions were similar to the Roth spots seen in patients with bacterial endocarditis, and that they were toxic and not embolic in origin Maumenee (168) described the

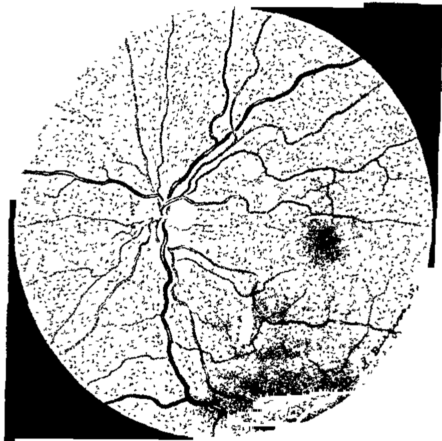


Fig 16 Typical cytoid bodies in the retina of a patient with SLE The nature of the lesions was confirmed by histological examination

ophthalmological and histological findings in the fundi of five cases and noted five types of lesions: 1) small, fluffy, yellowish-white to white spots located in the superficial layers of the retina, never larger than the size of the disc, usually in the posterior part of the fundus, similar in appearance to the cotton-wool exudates seen in hypertensive retinitis. Histologically, these lesions were demonstrated to be typical cytoid bodies in the nerve fiber layer of the retina (Fig 16) 2) Small superficial retinal hemorrhages related neither to the larger retinal vessels nor to the white spots Histologically, these were found in the nerve fiber layer of the retina 3) Slight papilledema, never of sufficient degree to allow actual measurement of an elevation of the disc. 4) A slight generalized blurring of the choroidal reflex believed to represent sub-retinal edema 5) Septic choriditis which could not be detected ophthalmoscopically but was noted on histological study as a slight round cell infiltration of the choroid in every case.

Jessar and his group (129) noted retinal lesions in 20 per cent of their series,

TABLE V

✓*Ocular manifestations seen in 105 cases of systemic lupus erythematosus*

✓Lesion	Number of Patients
Cytoid bodies	26
Conjunctivitis	5 (2 of these had repeated episodes of follicular conjunctivitis)
Exudates	6
Occlusion central retinal vein	2 (1 with hypertensive cardiovascular disease)
Small hemorrhages	11 (2 had uremia, 1 severe anemia)
Capillary aneurysms	1 (during intensive ACTH treatment)
Episcleritis	2
Papilledema	2 (both with convulsions—1 had azotemia and hypertensive cardiovascular disease)
Retinal hemorrhages with blindness	1

six patients having cotton-wool exudates, five flame-shaped hemorrhages, one retinal edema, one vasculitis with irregular beading, and one punctate corneal erosion. Hollenhorst and Henderson (120) have recently reviewed the ocular manifestations in SLE, and the alterations found included superficial retinal exudates, hemorrhage, papilledema, embolic petechiae, perivasculitis, and arterial occlusion.

It is our impression that when included with other suggestive clinical manifestations which may not be diagnostic, the finding of retinal cytoid bodies in the absence of hypertension or diabetes is a helpful point in the differential diagnosis of SLE. These lesions may be transient and repeated funduscopic examinations should be carried out during the course of the illness

Table V lists the ocular lesions found in our cases This does not give a true picture of the incidence of cytoid bodies as many of the patients seen early in the series had only a single eye examination

VII. HEMATOLOGICAL MANIFESTATIONS

Hematological abnormalities occur in virtually all cases of SLE at some time during the course of the disease The appearance of the L.E. cell is the only specific change, but other alterations in the formed elements of the blood constitute a fairly characteristic pattern. In occasional cases, these aberrations are the outstanding and at times the presenting manifestations. In such instances the nature of the underlying disorder may be overlooked, and the patient thought to have a primary blood dyscrasia.

a Red Cells

The high incidence of anemia in SLE has been frequently emphasized (5, 176). In a detailed report of blood changes in 111 cases Michael, Vural, Bassen and Schaefer (172) noted that only 25 patients had hemoglobin values of 12 grams per 100 ml. or higher at the time of the first examination In 32 cases the value

was between 10 and 11.9 grams, in 37 cases between 8.0 and 9.9 grams and in five cases below 6 grams. Of 16 patients who had initially normal hemoglobin values 15 subsequently developed anemia. The degree of the anemia seemed to be related to the duration and severity of illness. It was usually normocytic and normochromic. A similar anemia was present in 33 of the 34 cases reported by Shearn and Pirofsky (234), and in 11 of these the hemoglobin concentration was less than 9 grams per 100 ml. In a group of 323 cases Jessar, Lamont-Havers and Ragan (129) found anemia (below 12 grams) to be present at some time during the disease in 80 per cent. Forty-eight of Dubois' (56) 62 patients had hemoglobin values below 11 grams.

The anemia in most cases appears to be the result of retarded erythropoiesis. The decreased production of red cells is not associated with morphologic evidence of erythroid hypoplasia of the bone marrow (vide infra). The absence of jaundice, reticulocytosis and erythroid hyperplasia of the marrow in the majority provides evidence that the anemia is not primarily hemolytic in character. Hemorrhage, renal insufficiency and the presence of superimposed infection may contribute to the severity in some cases.

Moderate normocytic, normochromic anemia was commonly encountered in our cases. Seventy per cent were anemic when first examined, and 78 per cent are known to have had anemia at some time during the course of the disease. Analysis of 120 cases revealed that 36 had initial hematocrit values of 36 per cent or greater (hemoglobin 12 grams per 100 ml or more), 64 had values between 30 and 35 per cent, 17 between 24 and 29, and only three under 24 per cent. Of the group who initially had no appreciable anemia (hematocrit 36 per cent or over), ten subsequently became anemic. In a few, however, the disease ran its course and terminated fatally without the development of subnormal hemoglobin values. Profound anemia occurred in some in association with hemorrhage, renal insufficiency or a hemolytic process. Thirty-five per cent of the patients were transfused on one or more occasions. Once anemia became established, there was, in general, little tendency for it to progress, and most patients had only moderate lowering of hemoglobin even in the terminal stage of the disease. A few showed striking spontaneous improvement in hemoglobin concentration, the blood values sometimes returning to normal.

[illegible] showed minor red cell abnormali- [illegible] ells, [illegible] in a [illegible] not [illegible] elevated except in association with hemolytic anemia, after hemorrhage, or during hormone therapy. In rare instances a few nucleated red cells were seen [illegible] patients none [illegible] value [illegible] SLE [illegible] cytes [illegible] rried [illegible] out.

Although anemia usually appeared to result from retarded erythropoiesis, only one patient had a true hypoplastic anemia.

This patient (Case 6), who had had a polyarthritis, developed purpura associated with anemia, neutropenia, thrombocytopenia, and hypoplastic marrow. These manifestations appeared after a second course of chloramphenicol. L.E. cells were repeatedly demonstrated. Although some granulocytes have appeared, she continues to have anemia, leucopenia and thrombocytopenia three years later

In occasional cases a hemolytic process may occur as an important manifestation of SLE (23, 44, 55, 83, 151, 172, 177, 199, 234). This type of anemia is uncommon, occurring in less than 5 per cent of reported cases Hemolytic anemia, *when it occurs, may be the initial manifestation or may appear later.* In those instances in which it preceded other evidences of SLE, a diagnosis of "idiopathic" acquired hemolytic anemia was made. Of interest in this regard is a case reported by Lee, Michael and Vural (156) who considered the finding of L. E. cells in a patient with acquired hemolytic anemia a "false positive" result because other manifestations of SLE were not present.

In all of the reported cases of hemolytic anemia, hemoglobin values below 6 grams were recorded, and onset of the process has been acute Data of well documented reported cases and three of our own are included in Table VI Reticulocytosis of marked degree and normoblastic hyperplasia of the bone marrow have been uniformly observed The spleen has been palpable in most instances and enlarged in every case in which the weight was reported However, characteristic anatomical lesions of SLE were not always present Red cell auto-agglutinins or a positive Coombs test have been demonstrated in most cases Hemoglobinemia and hemoglobinuria have been described in a few instances. Spherocytosis of the red cells has been reported only once. In the few cases in which splenectomy was performed, no appreciable effect on the hemolytic process was observed, but administration of ACTH or cortisone has been effective in inducing remission in several patients The Coombs' test may remain positive even though complete hematological remission occurs during cortisone administration (199). Pisciotta and his associates (199) demonstrated that the L.E. factor in serum can be separated from the substance which is absorbed on the red cells and which gives rise to the positive Coombs' test In occasional cases, including one of our own, *severe hemolytic anemia first appeared following the administration of blood* transfusions (125, 151).

Hemolytic anemia was present in three of our cases (Table VI). In one, a fulminating hemolytic process with hemoglobinuria first appeared long after the onset of other manifestations of SLE This patient is of interest because splenectomy was performed two years before the onset of anemia:

Case 30

I C (#A-47972), a 13 year old colored girl, had a positive serologic test for syphilis (STS) in the absence of syphilitic manifestations at age seven Both parents had a positive STS At age 11 she developed severe thrombocytopenic purpura She had had intermittent pain in the elbows and knees for seven months There was considerable loss of blood from nose

TABLE VI

Hemolytic anemia in SLE

Source	Patient	Palpable Spleen	Osmotic Fragility	Auto-agglutinins	Coombs' Test	Hemoglobinuria	Response to Splenectomy	Response to ACTH or Cortisone	Splenic Lesion
1. Pisciotta, Gilberti, Greenwalt and Engstrom (109)	15 WF	Yes	—	Cold aggl. 1 32	Direct pos , indirect neg	No	—	Complete hematologic remission on cortisone	—
2 Michael, Vural, Bassen and Schaefer (172)	42 WF	Yes	Normal	None	Neg	Yes	—	—	—
3 Michael, Vural, Bassen and Schaefer (172)	10 WF	Yes	—	Cold aggl present	—	No	Transient favorable response	—	No lupus lesions
4 Michael, Vural, Bassen and Schaefer (172)	34 WF	Yes	—	—	Pos	No	—	—	—
5 Dubois (55)	8 WF	Yes	Normal	—	Pos direct	No	None	Complete remission on ACTH	Weight 387 Gm. Periarterial fibrosis
6 Dubois (55)	17 WF	No	Normal	Neg cold aggl	Pos direct and indirect	No	—	Complete remission on ACTH	—
7 Dubois (55)	13 WF	Yes	Normal to slightly increased	Cold aggl pos 1 2000	Pos direct	No	None	No response to ACTH, 30 mgm daily	Weight 610 Gm Typical lupus lesions
8 Shearn and Pirofsky (234)	25 WF	Yes	—	—	Pos	No	—	No response ? Inadequate trial	—
9. Kuhns and Bauerlein (151)	15 WF	Yes	—	Present	—	Yes	—	—	Weight (autopsy) 350 Gm Periarterial fibrosis
10 Dubois (56)	46 WF	No	—	Present	Neg direct and indirect	No	—	No response	Weight (autopsy) 430 Gm Typical lupus lesions Periarterial fibrosis
11 JHH #A-47972 (Case 30)	18 CF	Previously removed		Present	—	Yes	Spleen previously removed	—	
12. JHH #473642 (Case 12)	37 CF	No	—	None	—	Ye	—	—	Weight (autopsy) 200 Gm Hemosiderosis
13 JHH #505022 (Case 31)	34 WF	Yes	Normal	Present	Pos direct	No	None	Complete remission on ACTH Prompt relapse when treatment discontinued	Weight 185 Gm No lupus lesions

and gums The hematocrit was 23 per cent, white cells 6300 and platelets 12,000. Splenectomy was performed, the spleen weighing 148 gm and showing the typical periarterial [illegible] SLE There was a prompt rise in the platelet count to normal values and thrombocytopenia never recurred She developed a transient pericardial effusion postoperatively. Six [illegible] after splenectomy the hematocrit was 40 per cent, white count 6000 and the platelet [illegible] 228,000 Six months later, she developed joint manifestations typical of [illegible] arthritis At this time hematocrit was 41 2, white count 5400 and platelet [illegible] The polyarthritis subsided and she was well for the next year, when she returned with facial eruption typical of SLE, polyarthritis, generalized lymphadenopathy and [illegible] The hematocrit was 44, but under observation the patient developed [illegible] with a rapid fall in hemoglobin concentration The red cells showed [illegible] agglutination but Donath-Landsteiner and Ham tests were negative [illegible] and hemoglobinuria persisted until death Autopsy showed widespread lesions of SLE and there was no accessory splenic tissue found

The mechanism of the hemolytic anemia in SLE has not been [illegible] Dubois (55) suggested that it might be hypersplenic in origin. However [illegible] reports that splenectomy has little or no effect on the rate of blood [illegible] together with our observation that the hemolysis in one patient [illegible] splenectomy leave little to support this hypothesis. A more likely [illegible] that the process is the result of an abnormal protein which may [illegible] and lead to their destruction. Whether this abnormal protein is a [illegible] antibody is not known. It has been repeatedly demonstrated, however [illegible] serum of some patients with SLE may cause agglutination of normal [illegible] well as the red cells of the patient That the abnormal protein [illegible] cell is indicated by the positive direct Coombs' test not infrequently [illegible] in these patients, and the positive indirect Coombs' test which [illegible] tained Striking autoagglutination of the red cells, and a positive Coombs' may occur in SLE in the absence of detectable evidence of [illegible] destruction. Severe autoagglutination was noted in two of [illegible] by Aegerter and Long (1). Evans and co-workers (67) found a [illegible] test in each of four patients with SLE, although none showed [illegible] creased blood destruction, while the test was positive in [illegible] amined by Zoutendyk and Gear (279, 280). The Coombs' test [illegible] approximately 25 per cent of the cases (number of cases [illegible] Rosenfield and Vogel (222). Three of four patients on whom [illegible] formed had a positive result in the study of Shearn and [illegible] three were suspected of having a hemolytic anemia.

The Coombs' test was performed on 34 of our patients, [illegible] hemolytic anemia. The test gave positive results in [illegible] indirect test was also positive. Agglutination of the red [illegible] albumin was demonstrated in two cases with positive [illegible] others, but did not occur in the four additional patients [illegible] with positive Coombs' tests

Extraordinary autoagglutination of red cells was [illegible] cases and was particularly pronounced in five, only [illegible] anemia Immediately after blood was drawn, [illegible] patient, examined with the slit lamp and [illegible]

seen to flow through the conjunctival vessels in aggregates. This patient had a peculiar mottling of the skin thought to result from the intravascular clumping of red cells, but there was no evidence of increased blood destruction. Cold agglutinins were present in significant titer in three cases, including one with hemolytic anemia, but one patient with pronounced manifestations of Raynaud's syndrome had no demonstrable cold agglutinins or cryoglobulins.

Some patients with SLE seem to have a remarkable ability to develop antibodies against red cell antigens Callender, Race and Paykoc (36, 37) reported a case in which multiple transfusions were followed by the demonstration of five separate antibodies including three which were previously undescribed. Five atypical antibodies were found in the serum of another patient with probable SLE (265). Anti-Kell antibody has been demonstrated in a patient with the disease after transfusions (225). A patient with SLE who developed hemolytic anemia following multiple transfusions was reported by Kuhns and Bauerlein (151) to have three atypical hemagglutinins. In other instances hemoglobinuric transfusion reactions have been attributed to Rh isosenitization (8).

Several authors have commented on the frequency of transfusion reactions in patients with SLE. In three of the nine cases reported by Aegerter and Long (1) transfusions were followed by reactions not attributable to ABO or Rh incompatibility. In the patients studied by Michael, Vural, Bassen and Schaefer (172) transfusion reactions seemed to be more common than in the general hospital population. In some instances these were ascribable to the development of atypical isoagglutinins (204).

More than 200 transfusions have been given to 39 patients in our series. The frequency of untoward reactions has been low. Occasionally there has been a brief febrile response or urticaria, but patients displaying these manifestations have subsequently been transfused without repetition of the reaction. One patient had a hemolytic episode with hemoglobinuria following a transfusion of apparently compatible blood. However, he received blood on numerous occasions before and after this episode without reaction. Atypical hemagglutinins were demonstrable in the serum of several patients, who did not have transfusion reactions. The serum of one patient contained a peculiar hemagglutinin which did not correspond to any of the recognized red cell antigens. In a few instances multiple isosensitization was demonstrated.

b. White Cells

In the cases reported by Goeckerman in 1923 (80) leucopenia was frequently present and at times severe. Since then numerous observers have reported abnormalities in the white cell count with leucopenia (white count below 6000) being observed in from 25 to 85 per cent of the cases Extreme leucopenia (below 2000) has been unusual. Deviation of the white count from the normal range has ... to 30,000 ...vation of ... when the

initial phase is severe (5, 6, 56, 129, 160, 172, 221, 254).

depression of the platelet count has been of only moderate degree In some cases, however, thrombocytopenia increased with the severity of the disease In one series of 83 cases (172) 34 had platelet counts below 150,000 when first examined and 43 were known to have had thrombocytopenia at some time However, severe bleeding occurred in only one case. Marked thrombocytopenia was present in six of 62 cases in another series (56).

Information concerning the platelets is available in 86 of our cases In 23 of these platelet counts at times were definitely abnormal Twelve patients had severe thrombocytopenia, with counts of less than 50,000 per cu mm This group includes those cases in which thrombocytopenic purpura was the outstanding manifestation of SLE. Seven other patients had platelets between 50,000 and 100,000 per cu. mm but abnormal bleeding was not impressive. In four cases counts ranged between 100,000 and 150,000 The remaining 63 showed no evidence of platelet deficiency A few patients developed thrombocytopenia as the disease progressed toward the terminal stage, but in many, platelets remained abundant until death

In occasional cases of SLE thrombocytopenic purpura is the outstanding feature of the disease The hemorrhagic disorder may occur when other manifestations are trivial, or may actually antedate them by months or years. These patients have been thought to have "idiopathic" thrombocytopenic purpura, and the platelets may return to normal either spontaneously or as a result of splenectomy Data from 13 cases of this type collected from the literature and nine cases from our own series are presented in Table VIII It will be noted that in many cases no symptoms preceded the occurrence of thrombocytopenia. Other manifestations of SLE first appeared as long as seven years after the onset of purpura. In six cases typical discoid lupus had been present before the onset of thrombocytopenic purpura, but in some of these the appearance of other manifestations of SLE was long delayed It is noteworthy that the thrombocytopenic purpura occurring in this disease may be clinically indistinguishable from "idiopathic" thrombocytopenic purpura There may be no anemia other than that accounted for by hemorrhage, the white cell count may be normal, the spleen may not be palpable, and the bone marrow pattern is typical of "idiopathic" purpura. Furthermore, splenectomy has been regularly followed by elevation of the platelet count, often to normal levels. In most patients subjected to this procedure, there has been no recurrence of thrombocytopenia even though death from SLE ultimately occurred In most recorded instances the weight of the spleen was increased. Periarterial fibrosis in the spleen was not uniformly demonstrable, even though searched for carefully.

In 1949 Rich (215) reviewed cases at the Johns Hopkins Hospital in which a clinical diagnosis of "idiopathic" thrombocytopenic purpura had been made, and in which the spleen was available for microscopic examination. In six periarterial fibrosis was noted. Two of the six patients developed clinical evidences of SLE and died more than two years after splenectomy had been performed

morphonuclear cells was often associated with a moderate shift to the left. Thirty per cent of our patients had more than 5 per cent juvenile neutrophils, and a few had as many as 20 per cent. It was not unusual to find an occasional myelocyte in the blood; in four cases the number ranged between three and eight per cent

Data pertaining to eosinophils were tabulated for 106 cases prior to therapy. In 46 of these, differential cell counts had been performed, but direct eosinophil counts had not been made. No eosinophils were seen in the blood smears in 17 cases. In 13 others as many as two per cent were counted at times. Seven patients had as many as three to four per cent eosinophils and six had five to eight per cent. Only two patients had higher proportions: one with 17 and one with 24 per cent. Pronounced eosinophilia was associated with extensive skin lesions, and was not attributable in these cases to detectable causes other than SLE. Direct eosinophil counts were available in 60 cases. The number was less than 50 per cu. mm. in 31 cases; between 50 and 100 in 11, and between 100 and 200 in ten. Six patients had between 200 and 400 eosinophils per cu. mm., and only two had counts in excess of 400.

Atypical lymphocytes were often present in small numbers, usually comprising not more than one per cent of the white cells. However, two patients had eight and nine per cent atypical lymphocytes.

Two of our patients transiently had severe granulocytopenia In one the neutropenia was associated with a hypoplastic anemia which was thought due to chloramphenicol. In this case the total white count was 1600 with 91 per cent lymphocytes and only five per cent granulocytes. One other patient with SLE was thought to have acute agranulocytosis at the time of admission. She had a white cell count of 2600 with 78 per cent lymphocytes, six per cent juvenile neutrophils and six per cent polymorphonuclear cells. There was a history of recent ingestion of several headache remedies. Granulocytes appeared in normal proportion within a few days at a time when the SLE was rapidly progressing

c. Platelets

Purpura has often been encountered in SLE and was described by Kaposi (135), Osler (189) and numerous other authors. Each of the four patients of Libman and Sacks (160) had prominent petechial and other hemorrhagic manifestations, and one is known to have had thrombocytopenia. Keil (138) in 1937 reviewed the earlier literature on the hemorrhagic tendency in this disease and pointed out that several mechanisms are involved including vascular factors, azotemia and thrombocytopenia. Purpuric spots, petechiae, hemorrhagic vesicles and bullae, bleeding into the mucous membranes, from the nose, gums and from the gastrointestinal tract were described. Platelet counts were not recorded in many case studies, but more recent evidence indicates that the purpuric bleeding [illegible] f 100 patients with SLE

Nevertheless, thrombocytopenia has been observed in many cases ([illegible] 56, 61, 75, 78, 133, 134, 160, 163, 172, 221, 234, 251, 258, 272). In most instances

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In 1949 Rich (215) reviewed cases at the Johns Hopkins Hospital in which a clinical diagnosis of "idiopathic" thrombocytopenic purpura had been made, and in which the spleen was available for microscopic examination In six periarterial fibrosis was noted Two of the six patients developed clinical evidences of SLE and died more than two years after splenectomy had been performed. Autopsy in one case showed visceral and cutaneous lesions of SLE One other patient, not suspected clinically of having SLE, had visceral lesions of this disease at autopsy

TABLE VIII

Thrombocytopenic purpura in SLE

Source	Patient	Antecedent Manifestations	Palpable Spleen	Platelets	Hgb	WBC	LE Cells	Effect of Splenectomy	Effect of ACTH or Cortisone	Splenic Lesion	Ultimate Outcome
1 Wise (272)	18 WF	None Thrombocytopenic purpura for four years	?	?	?	?	—	Immediate cessation of purpura	—	—	6 months after splenectomy developed cutaneous lupus, fever, nephritis and died Platelets remained normal
2. Lyon (163)	12 M	Intermittent thigh pain, fever and erythematous rash for two months	yes	22,000	80%	3600	—	—	—	Weight 323 Gm No lesions described	Platelets returned to normal spontaneously after one month but patient died of SLE
3 Jones and Tocantins (135)	F	None recorded	?	20,000	?	5000	—	Platelets returned to normal in 3 months	—	?	Developed cutaneous lupus 5 months after splenectomy
4 Milbradt (173)	13 WF	Cutaneous lupus	no	10,000	38%	5000	—	—	—	—	Died of intracranial hemorrhage
5 Keil (138)	18 WF	None Thrombocytopenic purpura for four months	?	1,000 to 69,000	66%	18,800	—	Purpura subsided promptly	—	Twice normal size	Developed cutaneous lupus 2 years after splenectomy. Died of SLE 7 years post-op Platelets prior to death 200,000
6 Edelman (61)	49 WM	Discoid lupus of face for two years	no	30,000	37%	7500	—	—	—	Slightly enlarged. Hyalinization of arterioles	Died of hemorrhage Autopsy showed lupus lesions in kidney
7. Brady and Neal (30)	30 WF	Butterfly rash, nephritis, fever for 8 months	no	7100	66%	5200	—	Immediate cessation of bleeding Platelets rose to 144,000	—	Slightly enlarged. No lesions	No recurrence of thrombocytopenia in one year. Other manifestations of SLE persisted
8 Ottaviani and Pessarosa (190)	16 WF	Acute thrombocytopenic purpura at age 8 with persistent bruising tendency thereafter	yes	20,000	85%	7200	—	—	—	Periarterial fibrosis	Discoid lupus at age 13, recurrence at 16 with fever, petechiae, hematuria, coma, death. Megakaryocytes increased in marrow
9 Michael, Vural Bassen and Schaefer (172)	31 WF	None	?	?	?	?	Pos	Cessation of bleeding	—	?	Well for 7 years after splenectomy, then developed SLE and died Platelets prior to death 245,000

10 Michael, Vural Bassen and Schaefer (172)	27 WF	Facial eruption for three years	?	10,000	?	?	—	Cessation of bleeding Platelets returned to normal	—	?	Developed manifestations of SLE 2 years after splenectomy and died
11 Friedman, Kleinschmidt and Schwartz (75)	14 CM	Cutaneous lupus, fever for four weeks	yes	2300	40%	6300	Pos	—	Platelets returned to normal during therapy with ACTH and cortisone, but subsequent relapse failed to respond	?	Died after several weeks, presumably of SLE
12 Johnson (130)	37 WF	Discoid lupus for 12 years, malaise arthralgia	?	3000	8.4 Gm	3000	—	Rise of platelet count in 48 hours, eventually to 393 000	—	Weight 140 Gm	Blood normal 7 years after splenectomy Arthralgia and facial erythema persisted
13 Johnson (130)	22 WF	?	?	16 000	9.2 Gm	4000	—	Platelets rose to 140,000 in 24 hours	—	?	Platelets rose to 543,000 Died following massive hemorrhage from splenic pedicle 10 weeks post-op
14 JHH #60165	49 WF	None Purpura for one year	no	10,000	9.7 Gm	3850	—	—	—	Periarterial fibrosis	Died of hemorrhage
15 JHH #505022 (Case 31)	34 WF	Urticaria for many years Arthralgia for 8 years Thrombocytopenic purpura for 20 months	yes	53,000	11.9 Gm	5000 to 7000	Pos	Platelets promptly returned to normal	No rise in platelet count during ACTH, 100 mg daily for 4 weeks	Weight 185 Gm No periarterial fibrosis	No recurrence of thrombocytopenia Platelet count two years after splenectomy 435,000 Mild hemolytic anemia persisted
16 JHH #A 47972 (Case 30)	13 CF	Arthralgia for 7 months	no	12,000	8 Gm	6300	—	Platelets promptly returned to normal	—	Weight 148 Gm Periarterial fibrosis	No recurrence of thrombocytopenia Patient died of lupus 2 years after splenectomy, and terminally had hemolytic anemia
17 JHH #214623	19 WM	Butterfly rash on face, treated with gold, followed by appearance of purpura, 17 months before admission	no	18,000	8.7 Gm	5900 to 27,000	—	—	—	Weight 420 Gm (autopsy) Periarterial fibrosis	Died 22 months after onset, of combined effects of systemic lupus and hemorrhage. Bone marrow at autopsy hyperplastic with many megakaryocytes

TABLE VIII—*Continued*

Source	Patient	Antecedent Manifestations	Palpable Spleen	Platelets	Hgb	WBC	L E Cells	Effect of Splenectomy	Effect of ACTH or Cortisone	Splenic Lesion	Ultimate Outcome
18 JHH #207012	36 WF	Mild urticaria for years Purpura for 5 weeks Acute arthritis of knee *followed onset of* purpura.	no	<50,000	11.2 Gm	6200	Neg	Platelets returned to normal within 4 days	—	3 times normal size Periarterial fibrosis	Remained well with normal platelet count for 14 years, then had fulminating recurrence of purpura and died of *intracranial hemorrhage*
19 JHH #274052	39 WF	Recurrent rash of lupus on face for 8 years without other manifestations Purpura for 1 year.	no	30,000	10 Gm	4300 to 5500	—	Prompt rise in platelet count within 24 hours	—	Weight 154 Gm Periarterial fibrosis	*No recurrence of purpura.* Developed fulminating acute lupus 3 years after splenectomy. Died of pneumococcal septicemia
20 JHH #581252	37 WF	Urticarial reaction to penicillin 7 years before Three transient episodes of pleurisy Purpura for 5 weeks	yes	12,000	15 Gm	5900	Neg	Prompt cessation of bleeding Platelets 87,000 on 5th day	—	Weight 145 Gm. Periarterial fibrosis	No recurrence of purpura. Developed transient pleuritic pain, transient painful swelling of fingers within year after splenectomy Platelet count 274,000, 16 months after splenectomy
21. JHH #274379	61 WF	Pain in knees and elbows 9 years before. Severe purpura for 2 months	yes	12,000	9 Gm	4400	Neg	Prompt rise in platelets within *24 hours to 348,000* by 6th day.	—	Weight 300 Gm Periarterial fibrosis	No recurrence of purpura. Had pericarditis and fever *postoperatively. Appeared* well 2 years after splenectomy.
22 JHH #23565	22 WF	Transient arthralgia, fingers, elbows, knees of 1 year Purpura 4 weeks, 5 months pregnant.	yes	50,000	56%	8900	—	—	—	Weight 170 Gm Periarterial fibrosis	Died in 3 weeks of intracranial hemorrhage Kidney lesions of lupus and many megakarocytes in marrow at autopsy

Rich believes that pronounced periarterial fibrosis of the spleen rarely, if ever, *occurs in conditions other than SLE.*

✓The occurrence of thrombocytopenic purpura as an early manifestation of the disease is not rare. In the discussion which followed the report by Montgomery and McCreight (176), three cases were mentioned *in* which thrombocytopenic purpura treated by splenectomy had preceded other manifestations of SLE. In two of the cases of Gold and Gowing (83) thrombocytopenic purpura antedated other evidences of SLE by several years. A patient described by Dameshek and Rheingold (50) *as having "idiopathic" thrombocytopenic purpura was noted to* have had a painful polyarthritis associated with a "butterfly" rash of lupus erythematosus five years before the onset of abnormal bleeding. *It* is clear that a previous history of joint pain, pleurisy, skin eruption or other manifestations may have great significance in a patient with thrombocytopenic purpura. This is illustrated by one of our own cases:

Case 51

M R (#505022), a 34 year old white housewife, has been under observation since early 1950 She has had episodes of urticaria since early adolescence At the age of 24 she developed *mild* aching and stiffness of fingers and knees with occasional swelling of the proximal interphalangeal joints At that time she was given liver injections for "anemia" At 26 she had toxemia of pregnancy with hypertension, which subsided after delivery of a stillborn child *In the following year she felt nervous and was given a* liver injection following which she developed severe *urticaria* Two years later, because of inability to become pregnant, she received injections of hormones During this therapy she developed menorrhagia *which persisted* Thereafter, she had profuse epistaxes *and cutaneous* ecchymoses Examination revealed no splenomegaly, but there was thrombocytopenia and the sternal marrow was said to be compatible with "idiopathic" thrombocytopenic purpura One year later there were numerous petechiae and ecchymoses The tip of the spleen was palpable, but there was no evidence of joint disease The platelet count ranged between 32,000 and 68,000 per cu mm She also had a mild hemolytic anemia associated with a positive Coombs' test and auto-antibody in the serum The hematocrit was 34 per cent and hemoglobin 11 9 grams, the serum bilirubin 1 5 mg per 100 ml , fecal excretion of urobilinogen increased, and reticulocyte counts as high as seven per cent Numerous L E cells were demonstrated Marrow smears contained many megakaryocytes with no evidence of platelet formation The white cell count ranged between 5000 and 7000 She was treated intensively with ACTH The hemolytic anemia subsided, the hematocrit value reaching 41 per cent, the white count rose to 17,000, but there was no rise in the platelet count and hemorrhagic lesions continued to appear *After* therapy was discontinued there was recurrence of arthralgia and the hematocrit and white count fell to pretreatment values The purpura persisted and five months later she returned for splenectomy The spleen weighed 185 gm , and showed no periarterial fibrosis. The platelet count rose within a few hours to 214,000 There has been no recurrence of purpura or of thrombocytopenia two years after splenectomy She has undergone a normal pregnancy, during which her joint manifestations subsided The cord blood as well as blood drawn from the newborn female child did not form L E cells, and the infant's platelet count at birth was 275,000 Two weeks after delivery, the patient had a transient episode of iritis and recurrence of her joint symptoms Nevertheless, she has remained remarkably well and at present is again pregnant

The✓mechanism by which thrombocytopenia is produced in SLE is unknown. Although splenectomy is usually followed by a sustained rise of the platelet count, there is *little* to suggest that the platelet deficiency is secondary to disease

TABLE VIII—*Continued*

Source	Patient	Antecedent Manifestations	Palpable Spleen	Platelets	Hgb	WBC	L.E. Cells	Effect of Splenectomy	Effect of ACTH or Cortisone	Splenic Lesion	Ultimate Outcome
18 JHH #207012	36 WF	Mild urticaria for years Purpura for 3 weeks *Acute arthritis of knee* followed onset of purpura	no	<60,000	11 2 Gm	6200	Neg	Platelets returned to normal within 4 days	—	3 times normal size Periarterial fibrosis	Remained well with normal platelet count for 14 years, then had *fulminating recurrence of purpura* and died of intracranial hemorrhage
19 JHH #274032	39 WF	Recurrent rash of lupus on face for 8 years without other manifestations. Purpura for 1 year.	no	30,000	10 Gm	4300 to 5500	—	Prompt rise in platelet count within 24 hours	—	Weight 154 Gm. Periarterial fibrosis	No recurrence of purpura. Developed fulminating acute lupus 3 years after splenectomy. Died of pneumococcal septicemia
20. JHH #581282	37 WF	*Urticarial reaction* to penicillin 7 years before Three transient episodes of pleurisy Purpura for 5 weeks	yes	12,000	15 Gm	5000	Neg	Prompt cessation of bleeding. Platelets 87 000 on 5th day	—	Weight 145 Gm Periarterial fibrosis	No recurrence of purpura. *Developed transient pleuritic pain, transient painful swelling* of fingers within year after splenectomy. Platelet count 274,000, 16 months after splenectomy
21 JHH #274379	61 WF	Pain in knees and elbows 9 years before *Severe* purpura for 2 months	yes	12,000	9 Gm	4400	Neg	Prompt rise in platelets within 24 hours to 346,000 by 6th day	—	Weight 300 Gm Periarterial fibrosis	No recurrence of purpura Had *pericarditis and fever* postoperatively. Appeared well 2 years *after splenectomy*.
22 JHH #23565	22 WF	Transient arthralgia, fingers, elbows, knees of 1 year. *Purpura* 4 weeks, 5 months pregnant.	yes	50,000	56%	5500	—	—	—	Weight 170 Gm. Periarterial fibrosis	Died in 3 weeks of intracranial hemorrhage Kidney lesions of lupus and many megakaryocytes in marrow at autopsy.

Rich believes that pronounced periarterial fibrosis of the spleen rarely, if ever, occurs in conditions other than SLE.

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pregnant, she received injections of hormones During this therapy she developed menorrhagia which persisted Thereafter, she had profuse epistaxes and cutaneous ecchymoses Examination revealed no splenomegaly, but there was thrombocytopenia and the sternal marrow was said to be compatible with "idiopathic" thrombocytopenic purpura One year later there were numerous petechiae and ecchymoses The tip of the spleen was palpable, but there was no evidence of joint disease The platelet count ranged between 32,000 and 68,000 per cu mm She also had a mild hemolytic anemia associated with a positive Coombs' test and auto-antibody in the serum The hematocrit was 34 per cent and hemoglobin 11 9 [illegible]

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The mechanism by which thrombocytopenia is produced in SLE is unknown. Although splenectomy is usually followed by a sustained rise of the platelet count, there is little to suggest that the platelet deficiency is secondary to disease

coagulation defect was not discovered. In two cases prolongation of the clotting time was associated with severe thrombocytopenic purpura. In one of these patients studied in detail the prothrombin concentration was normal, an assay for anticoagulant was negative, and no defect other than thrombocytopenia was discovered. One patient without hemorrhagic manifestations was found to have a persistently prolonged clotting time, at times considerably in excess of one hour, with adequate platelets and normal prothrombin. An anticoagulant assay in this case was negative, and the cause of the coagulation defect was not detected.

The prothrombin time was determined in 38 of our cases. In 25 it was normal. In seven there was moderate prolongation, indicating that prothrombin was reduced to about 50 per cent of normal. Six patients had marked prolongation of the prothrombin time, with estimated prothrombin concentrations of less than 30 per cent of normal. The most profound hypoprothrombinemia was encountered in the boy, previously mentioned, who had a hemorrhagic disorder associated with a long clotting time. Marked prolongation of the prothrombin time in one case was associated with cirrhosis of the liver and in another with hepatitis In the cases in which a circulating anticoagulant was demonstrated, prolongation of the prothrombin time was shown to be caused by the anticoagulant rather than by prothrombin deficiency. Administration of various Vitamin K preparations was without significant effect in these patients.

No hemostatic defects were demonstrated in many of the patients who had purpura and epistaxis. Even the capillary fragility test was usually negative, unless the platelets were severely reduced.

e. Bone Marrow

The bone marrow has been examined in a large number of cases of SLE since the discovery of the L.E. cell phenomenon. In most reports the description is limited to observations on the occurrence of L.E. cells in incubated preparations. Michael, Vural, Bassen and Schaefer (172) examined the marrow in 32 cases In only one was it hypocellular. An increase in the proportion of plasma cells was often present and in one case reached 18 per cent. Marked erythroid hyperplasia was noted in association with hemolytic anemia. In general, however, the marrow pattern was normal.

Smears of aspirated marrow were examined in 36 of our cases. L.E. cells were often seen when incubation *in vitro* preceded preparation of the smears, but were never encountered in direct smears. The marrow in most instances appeared to ...

patient had developed a hypoplastic anemia following the ...
chloramphenicol. Megakarocytes were markedly reduced, the proportion of myeloid cells was low, and there was an increase in lymphocytes. In other cases ... though there was pronounced
... n when the
... it and were

usually present in normal proportion when anemia was profound. There was a definite tendency towards an increase in the number of plasma cells in the marrow. The plasmacytosis was of only slight degree in most instances, and in 17 of the 36 cases ranged between one and five per cent. In two cases a marked increase in the proportion of plasma cells was noted, values of 11 and of 17 per cent being obtained. The abnormally high proportion of plasma cells, together with the tendency for the red cells to be agglutinated on the smears, at times presented a pattern which was rather suggestive of myeloma. In those patients with thrombocytopenic purpura, megakaryocytes were abundant, at times appeared immature, and showed no evidence of platelet formation. In the presence of hemolytic anemia, the proportion of nucleated red cells in the marrow was high.

In several cases surgical biopsy of the marrow was performed. In addition, sections were examined in all of the autopsied cases. The marrow was normally cellular or hyperplastic and megakaryocytes were present, even in those patients dying from thrombocytopenic hemorrhage.

VIII. THE L.E. CELL PHENOMENON

a Characteristics of the Cell

A typical L.E. cell consists of a mature polymorphonuclear neutrophil containing within its cell membrane a mass of homogeneous material which stains red-purple with Wright's stain. This mass is round or oval and is usually several times as large as a normal red blood cell Because of this inclusion, the L.E. cell is characteristically larger than a normal neutrophil, the segments of the nucleus are displaced to the periphery, and only a thin crescent of cytoplasm can be seen about the edge of the mass (Fig. 17). "Rosettes" are frequently found in association with L.E cells. These are aggregates of polymorphonuclear neutrophils surrounding masses of homogeneous material. Also noted are extracellular globules of the same homogeneous material. These free globules and the material at the centers of the "rosettes" possess the same staining characteristics as the material within the L E. cells.

The L.E cell was first described in 1948 by Hargraves and his associates (97), who identified these structures in concentrated bone marrow preparations in more than twenty-five cases of SLE. It soon became apparent (95) that the cell is not found in direct smears of marrow but is formed *in vitro* following aspiration. Haserick and Sundberg (111) corroborated these findings.

b Factors Responsible for Formation

Hargraves (95) and Haserick and Bortz (105) reported that L.E. cells could be produced by mixing plasma of a patient with SLE and normal bone marrow elements. The first report of L.E. cells in buffy coat preparations of peripheral blood was made by Sundberg and Lick (249). Moffatt, Barnes, and Weiss (174) reported that the cells could be produced in mixtures of the plasma of patients with SLE and either normal peripheral blood or concentrated normal white cells There is now general agreement (17) that at least three factors are necessary

for the formation of these cells: (1) a substance present in the plasma of many patients with SLE; (2) nuclear material derived from leucocytes and altered through the influence of the plasma factor; and (3) active phagocytic cells which engulf the altered masses of nuclear material.

The plasma factor has been demonstrated to be associated with the gamma globulin fraction (23, 109, 152, 156). It is an immunologically distinct component of the gamma globulin, for antibodies against it can be produced in rabbits (108).

It is readily destroyed by bacterial action, but when kept under sterile conditions will retain its potency for several months (95, 101, 156). Activity persists after heating plasma to 59°C., and is destroyed by heating to 65°C. (95, 101).

The plasma factor is not inhibited *in vitro* by the addition of testosterone, estradiol, progesterone, or cortisone (87, 101). Para-aminobenzoic acid inhibits L.E. cell formation, but the mechanism is unknown (101). The repeated use of active plasma seems to potentiate its effect upon normal marrow cells, and it has been suggested that the accumulation of proteolytic enzymes resulting from the breakdown of cells serves to accelerate the process of nucleolysis (23).

The L.E. factor may at times be demonstrated in body fluids other than plasma. Watson, O'Leary, and Hargraves (267) found neutrophils with inclusion bodies which resembled L.E. cells in the fluid of blisters made by the application of cantharides cerate to the skin of patients with SLE. Other observers have demonstrated them in pleural fluid, pericardial fluid, cerebro-spinal fluid, and urine (112, 149, 229, 261). Bridge and Foley (32) showed that the L.E. factor may cross the placenta.

The mode of action of the plasma L.E. substance is unknown. Interest has centered about its possible relationship to desoxyribosenuclease (DNase). Kurnick and his associates (152) estimated the activity of this enzyme in the serum of twenty-three patients with SLE and compared these values with the results of L.E. cell tests. In some instances the L.E. cell factor was demonstrable in serum devoid of DNase activity. Furthermore, destruction of the DNase activity by heat did not eradicate the L.E. factor. Henstell and Freedman (117) reported the finding of a substance in normal human polymorphonuclear cells and lymphocytes which inhibits DNase. Kurnick and his colleagues (153) also demonstrated this factor and in addition, found, in human leucocytes, an inhibitor of the L.E. cell phenomenon. These two factors were similar in that both were destroyed by proteolytic enzymes, but not by nucleolytic enzymes, neither permeated a cellophane membrane, and both had the same stability under temperature variation. These observers suggested that the depolymerization of desoxyribose-nucleic acid, which presumably occurs in the formation of L.E. cells, is due to a derangement of the intracellular DNase-DNase inhibitor system. It was postulated that the plasma L.E. factor may act to release intracellular DNase from inhibition.

The inclusion bodies of the L.E. cells, the central masses of the rosettes, and the free extracellular globules are believed to originate from the nuclei of leuco-



Fig. 17. Smears of the buffy coat of heparinized blood (A) and marrow (B) showing L.E. cells. Wright's stain. ×1000

cytes, although platelet or megakaryocytic sources have been suggested (109). *It is now widely accepted that these structures are composed primarily of nuclear materials which have undergone a distinct type of lysis under the influence* of the plasma L.E. factor.

In his original report, Hargraves (97) suggested the nuclear origin of the inclusion bodies because of the manner in which they reacted to the Feulgen reagent. Lee, Michael and Vural (156) found that the inclusion bodies stained positively with both Feulgen reagent and methyl green, suggesting the presence of desoxyribose-nucleic acid. They also obtained the Feulgen-methyl green ratios of these bodies, and the results indicated that much of the DNA was probably in the depolymerized form. These observations suggested that the inclusions might bear some relationship to the hematoxylin-staining bodies seen in tissue sections (78, 92, 143). Berman and his associates (23) agreed with Klemperer that the hematoxylin-staining bodies and the L.E. cell inclusions are identical by virtue of their morphology and tinctorial properties, but in their own studies of L.E. cell preparations did not find conclusive evidence for the presence of large amounts of depolymerized DNA. Dameshek and Bloom (49) found that the L.E. cell inclusion may contain ribosenucleoprotein of cytoplasmic origin, and did not find glycogen, lipids, acid or alkaline phosphatases.

Hargraves (97) observed neutrophils engulfing nuclear material in supravital preparations but did not provide details about the source of the nuclear masses. Moyer and Fisher (183) saw neutrophils engulfing lymphocyte nuclei. Rohn and Bond (218) described initial degeneration of nuclei of polymorphonuclear neutrophils to amorphous masses, following which intact granulocytes engulfed the globules. They did not observe autolysis of lymphocytes in their preparations. Stich, Feldman and Morrison (245) also concluded that the L.E. inclusion body originates from nuclei of polymorphonuclear neutrophils. They noted that the lobes of these cells became rounded and pyknotic, and the interlobar filaments disappeared. This produced a structure which they termed the "pre-L.E. cell". The rounded, homogeneous, deeply stained nuclei were then thought to be extruded from these degenerating neutrophils to be engulfed by other intact granulocytes.

The formation of L.E. cells has been studied by a number of other investigators (212). Rebuck and Berman (209) observed their evolution by applying serum from a patient with SLE to the abraded skin of normal subjects. By examination of cover slips removed at appropriate time intervals from the abraded area, they noted that the nuclei of polymorphonuclear neutrophils first underwent degeneration, then appeared as free masses, which were engulfed by other neutrophils. They thought that occasionally degeneration and swelling of a single lobe of a neutrophil might occur, thus producing an L.E. cell without the step of phagocytosis.

As noted by Hargraves (97) the phagocytic cell is almost always a mature polymorphonuclear neutrophil. However, metamyelocytes, band forms of neutrophils, mature eosinophilic and basophilic polymorphonuclear cells, and monocytes have been noted to participate in this phenomenon (156, 183, 218). Even

lymphocytes are said to be active by Berman and his associates (23), but this report has not been confirmed.

L E. cells are formed equally well in preparations containing heparin, oxalate or citrate (95), and can also be demonstrated in clotted or defibrinated blood or marrow (11, 13, 66, 87, 155). Suksta and Conley (248) and Eppes and Ludovic (66) used blood handled in silicone-treated equipment and found that L.E. cells were produced in the absence of both anticoagulants and blood coagulation.

L E. cell formation is considered to be an *in vitro* rather than an *in vivo* event, since these cells are not ordinarily seen in direct smears of blood or marrow. However, they occasionally have been found in post-mortem preparations (94, 185). Klemperer (144) found in post-mortem sections of the pleura a structure identical in appearance with the L.E. cell. Eppes and Ludovic (66) searched many direct smears of finger tip blood containing L E. factor and found only one neutrophilic leucocyte which appeared to be engulfing amorphous, pink-stained material, but the resemblance to an L.E cell was not complete. Chomet and his associates (42) found L.E cells in direct smears from a patient with fulminating SLE.

L.E cells are formed very rapidly *in vitro*, but a definite interval of time is required for their appearance. Haserick (101) made smears of an incubating specimen every 60 seconds and found leucocyte clumping first appearing at 5–6 minutes and L.E. cells at 12–13 minutes. Lee, Michael, and Vural (156) in similar studies found the cells after two minutes' incubation, but stated that the maxi-

Of the three factors necessary for the formation of L.E cells only the plasma substance need be obtained from a patient with SLE. The nuclear material and phagocytes can be derived from normal blood or bone marrow (95, 105, 106, 174), blood of patients with a variety of diseases including chronic leukemia (183), stored blood (69, 183), and blood or marrow of numerous mammals (23, 103) Ross and Wells (223) were unsuccessful in attempts to use pigeon marrow.

Several efforts have been made to produce L.E cells experimentally. Castillo and his associates (41) injected guinea pigs intraperitoneally with the blood of patients with SLE and reported that female animals lost weight and developed fever and leucopenia. Preparations of defibrinated blood of these animals contained structures which were thought to resemble L E. cells, and examinations of the tissues histologically showed abnormal alterations about blood vessels. These experiments were repeated in our laboratory by Schoenrich (228). Nine weekly injections of plasma from a patient with SLE did not cause weight loss, fever or leucopenia. Examination of preparations of the blood of the animals *before* and after the injections showed structures which superficially resembled L.E. cells, but typical cells were not seen. No lesions suggestive of SLE were seen in the tissues at autopsy, but the kidneys of one animal showed focal renal lesions resembling the hypersensitivity nephritis produced by injection of horse serum in rabbits.

Inderbitzin (122) described the production in normal blood of structures resembling L.E. cells by the use of anticoagulants of high molecular weight. The sodium salt of polyvinyl alcohol-polysulfonic acid ester (PVAS-Roche) and several related compounds, after incubation with normal gamma globulin, were said to induce the formation of these cells. Haserick (102) added certain fungi to dog bone marrow and noted the appearance of *structures resembling L.E. cells.* Kurnick and his associates (152) were unable to produce the cells by incubating normal leucocytes with bovine desoxyribosenucleic acid. Finch, Ross and Ebaugh (68) produced *antiserum against leucocytes. On addition of the antiserum to* leucocyte preparations, they observed clumping of the white cells, phagocytosis of intact or degenerate cells by other leucocytes, and the formation of structures "*indistinguishable from Hargrave's L E. cell*". On examination of their photographs and preparations, we are unable to find structures which we would identify as L.E cells. Although nucleophagocytosis is apparent, the engulfed nuclei have not undergone the peculiar hyalinization which is characteristic of an L.E cell. Zimmerman, Walsh and Heller (278) reported experiments similar to those of Finch and his associates. Nucleophagocytosis was prominent in their preparations Some cells showed homogeneous inclusions and were said to resemble L.E. cells.

c. Occurrence

The L.E cell test has been reported to be positive in a large proportion of cases of SLE. Some authors (103, 245) have obtained positive tests in 100 per cent, but most have encountered patients in whom the cells could not be demonstrated (155, 176, 234, 248). Dubois (57) found the test positive in only 48 of his 70 cases

L.E. cell tests were performed in 96 of our cases and were positive in 79, an incidence of 82 per cent. It is impossible to determine the true frequency of positive tests in SLE because there is no method by which the diagnosis can regularly be established with accuracy. In the absence of a positive test, the diagnosis often is not made. More than 50 patients examined at the Johns Hopkins Hospital were suspected of having SLE but were not included in the present series because proof of the diagnosis was lacking In all of these cases, L.E. cell tests were negative, often on repeated study. Nevertheless, many had typical clinical manifestations of SLE, and one patient who subsequently died was proved to have this disease at autopsy.

L.E. cells could not be demonstrated in 17 of our patients with unequivocal SLE. The disease was active in all and some were critically ill Histologic proof of the diagnosis was available in nine. Three patients had only a single test, but in the others as many as 12 examinations had been performed using heparinized blood, bone marrow, and in some clotted blood and guinea pig blood, all with negative results. In our experience the activity of the disease is not well correlated with the number of L.E cells. Some of our patients have had remissions lasting several years during which the cells were repeatedly demonstrable in considerable numbers

d. Techniques of L E. Test

A number of methods have been recommended for clinical use in the detection of L E. cells. Examination of the buffy coat of heparinized bone marrow has been largely supplanted by use of peripheral blood Buffy coat smears prepared from heparinized blood after incubation *in vitro* have been very satisfactory. Several investigators have preferred to examine buffy coat smears from defibrinated (66, 166) or clotted blood (85, 155, 277) It has been claimed by some (87, 155, 166, 277) and denied by others (57) that techniques employing clotted blood are more sensitive than those in which an anticoagulant is used. Hargraves (96) believed that platelets or their degradation products might augment L E. cell formation. However, two of our patients with severe thrombocytopenia were repeatedly found to have L.E cells in buffy coat preparations Splenectomy in one case was followed by a tremendous rise in platelet count but was without effect on the number of L E. cells Even the proponents of the clotted blood technique admit that the preparations tend to be hypocellular, that there is much cellular distortion and that nucleophagocytosis is increased As a result these preparations are more difficult to interpret than are those of heparinized buffy coat We have never been able to demonstrate L E cells by use of the clotted blood technique when they were not detected using heparinized blood. The addition of the patient's plasma or serum to cells obtained from normal blood or marrow is a more cumbersome technique which is of particular value when the patient has pronounced granulocytopenia Animal blood or marrow has been preferred by some investigators (103)

Regardless of the technique used in the preparation of the smears, great care is required in their examination L E cells may be overlooked unless a diligent search is pursued Phagocytosis of erythrocytes, of intact white cells, or of cell nuclei is often encountered in buffy coat preparations, and the resulting structures may resemble L E cells Therefore, rigid criteria should be used for their identification. Special attention should be given to the intracellular inclusion body, which is structureless, hyaline and homogeneous in appearance

Repeated examinations may be necessary in order to obtain a positive test. In one of our cases, 18 studies were performed during a two year period but only two were positive Another patient had 12 negative tests during a prolonged period of active disease before L E cells were finally demonstrated In this case, extracellular masses of hyaline material had repeatedly been noted

e L.E Cells in Other Diseases

Isolated cases have been encountered in which L.E cells were said to have been found in the absence of other evidences of SLE. False positive tests have been reported in one case each of pernicious anemia (23), dermatitis herpetiformis (23), leukemia (69), miliary tuberculosis (156), candida albicans infection (76), myeloma (3), acquired hemolytic anemia (156) and glomerulonephritis (192) In the case of acquired hemolytic anemia, it seems not unlikely that the hemolytic process was a manifestation of SLE, and the patient with glomerulo-

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d Techniques of L E. Test

A number of methods have been recommended for clinical use in the detection of L E. cells Examination of the buffy coat of heparinized bone marrow has been largely supplanted by use of peripheral blood Buffy coat smears prepared from heparinized blood after incubation *in vitro* have been very satisfactory. Several investigators have preferred to examine buffy coat smears from defibrinated (66, 166) or clotted blood (85, 155, 277). It has been claimed by some (87, 155, 166, 277) and denied by others (57) that techniques employing clotted blood are more sensitive than those in which an anticoagulant is used Hargraves (96) believed that platelets or their degradation products might augment L E cell formation. However, two of our patients with severe thrombocytopenia were repeatedly found to have L.E cells in buffy coat preparations. Splenectomy in one case was followed by a tremendous rise in platelet count but was without effect on the number of L.E cells. Even the proponents of the clotted blood technique admit that the preparations tend to be hypocellular, that there is much cellular distortion and that nucleophagocytosis is increased. As a result these preparations are more difficult to interpret than are those of heparinized buffy coat We have never been able to demonstrate L E cells by use of the clotted blood technique when they were not detected using heparinized blood The addition of the patient's plasma or serum to cells obtained from normal blood or marrow is a more cumbersome technique which is of particular value when the patient has pronounced granulocytopenia Animal blood or marrow has been preferred by some investigators (103).

Regardless of the technique used in the preparation of the smears, great care is required in their examination L E cells may be overlooked unless a diligent search is pursued. Phagocytosis of erythrocytes, of intact white cells, or of cell nuclei is often encountered in buffy coat preparations, and the resulting structures may resemble L E cells Therefore, rigid criteria should be used for their identification. Special attention should be given to the intracellular inclusion body, which is structureless, hyaline and homogeneous in appearance

Repeated examinations may be necessary in order to obtain a positive test. In one of our cases, 18 studies were performed during a two year period but only two were positive Another patient had 12 negative tests during a prolonged period of active disease before L.E cells were finally demonstrated. In this case, extracellular masses of hyaline material had repeatedly been noted

e. L E. Cells in Other Diseases

Isolated cases have been encountered in which L.E. cells were said to have been found in the absence of other evidences of SLE False positive tests have [illegible]

(192). In the case of acquired hemolytic anemia, it seems not unlikely that the hemolytic process was a manifestation of SLE, and the patient with glomerulo-

nephritis had other manifestations suggestive of this disease. Amyloid in the bone marrow may give rise to structures similar to L.E. cells (256), and may have been responsible for the apparent false positive test in the case of myeloma. Phagocytosed nuclei may resemble these cells and probably account for some false positive results. Walsh and Zimmerman (266) demonstrated L.E. cells in three patients with severe reactions to penicillin At least one of these had had previous manifestations suggestive of SLE, and reactions to drugs are known to be common in this disease.

Slocumb (238) reported that L E cells had been found following withdrawal of cortisone in 15 patients thought to have rheumatoid arthritis and to whom sufficient hormone had been given to produce "hypercortisonism". There is no mention in this report of the results of L E. tests prior to therapy. In view of the great frequency with which polyarthritis is the presenting manifestation of SLE, the possibility must be considered that these patients had SLE prior to the administration of cortisone.

Recently a syndrome resembling SLE, occasionally associated with positive L.E. cell tests, has been described in patients with hypertension after prolonged treatment with hydrazino-phthalazine (60, 182, 196). The nature of this syndrome and its relation to SLE remain to be clarified.

In several large surveys, no false positive tests were found among hundreds of patients with diseases other than SLE (57, 103, 156, 165, 167, 223, 245, 248). Uniformly negative results were obtained in periarteritis nodosa, scleroderma, rheumatic fever, various hypersensitivity reactions and many other disorders unrelated to SLE. L E. cell tests have been performed in our laboratory on many hundreds of patients. In every instance in which the cells were found, the patient had a clinical disorder which was compatible with the diagnosis of SLE. The clinical records of more than 700 patients with negative tests were reviewed, and the final diagnoses are shown in Table IX.

IX. PLASMA PROTEIN ABNORMALITIES

Abnormalities of the plasma proteins occur with great frequency in SLE. In some cases, protein disturbances have been detected years before clinical evidences of the disease appeared. The mechanism by which these changes are produced and their relationship to pathogenesis remain obscure. However, certain of the clinical manifestations of SLE are attributable specifically to plasma protein alterations.

a. Albumin and Globulin

Coburn and Moore (43), using the Howe technique, found the albumin fraction low and the globulin high in each of 17 patients. Abnormalities of the albumin-globulin ratio have been encountered frequently by other investigators and were noted in 69 per cent of the cases of Shearn and Pirofsky (234). Twenty-eight per cent of Dubois' patients (56) had serum globulin concentrations in excess of 3 8 gm. per 100 ml. Hyperglobulinemia (over 3 0 gm. per 100 ml.) was present in 42 per cent of 167 cases collected by Jessar and his associates (129).

TABLE IX

*Results of L.E cell tests performed in the hematology laboratories of the Johns Hopkins Hospital**

Diagnosis	Number of Cases Examined	Number Positive
Systemic lupus erythematosus	96	79
Undiagnosed disease with clinical and laboratory findings compatible with SLE, periarteritis or other connective tissue disease	83	0
Cutaneous lupus erythematosus without systemic manifestations	26	0
Scleroderma	7	0
Raynaud's syndrome	5	0
Periarteritis nodosa and temporal arteritis	9	0
Dermatomyositis	3	0
Rheumatoid arthritis	116	0
Felty's syndrome	3	0
Reiter's syndrome	1	0
Palindromic arthritis	4	0
Gonorrheal arthritis	3	0
Gout	2	0
Osteoarthritis	14	0
Arthritis, type and cause unknown	15	0
Rheumatic fever	38	0
Glomerulonephritis	16	0
Acute pleuritis and pericarditis	15	0
Diseases of the eye including uveitis, episcleritis, retinitis, choroiditis	21	0
Hypersensitive reactions to antibiotics including penicillin, horse serum, gold, blood transfusions	21	0
Allergic rhinitis, asthma, urticaria	14	0
Henoch-Schönlein purpura	4	0
Diseases of the skin including acne rosacea, seborrheic dermatitis, erythema multiforme, erythema nodosum, eczematoid and atopic dermatitis, exfoliative dermatitis, pemphigus, psoriasis	33	0
Gastro intestinal disorders including ulcerative colitis, regional enteritis, cholecystitis	10	0
Infections of many types including tuberculosis, leprosy, abscesses, miscellaneous bacterial and viral diseases	45	0
Neoplasms, malignant and benign	14	0
Anemias (aplastic, iron deficiency, pernicious, myelophthisic, hemolytic)	16	0
Acquired hemolytic anemia, "idiopathic"	4	0
Leucopenia, cause unknown	8	0
Hemophilia and pseudohemophilia	3	0
"Idiopathic" thrombocytopenic purpura	11	0
Thrombotic thrombocytopenic purpura	2	0
Leukemia, lymphoma, myeloma, myeloid metaplasia	17	0
Peripheral vascular disease	8	0
Endocrine disorders including diabetes, hyperthyroidism	12	0
Cirrhosis of the liver	10	0
Sarcoid	4	0
Amyloidosis	1	0
Neuromuscular diseases including epilepsy, peripheral neuritis, degenerative disease of muscle	11	0
Psychiatric disorders	26	0
Fever of undetermined origin	12	0

* All of these tests were performed by skilled research technicians who had no knowledge concerning the patient or the clinical diagnosis. Negative results were obtained in hundreds of other cases of miscellaneous diseases

Serum protein fractionations were performed in 105 of our cases and 58 per cent had globulin concentrations over 3.0 gm. per 100 ml. Values in excess of 4 gm. were not unusual, and in rare instances were as high as 8 gm. The concentration of albumin in the serum was less than 3.5 gm. per 100 ml. in approximately half of our cases, and in several instances was lower than 2.0 gm. Pronounced elevation of the plasma fibrinogen concentration was noted in the few cases in which this determination was made.

Coburn and Moore (43) performed electrophoretic analyses of the serum of two patients and found that the gamma globulin was elevated but alpha and beta fractions were normal. Electrophoretic studies were also done by Reiner (212) and by Walker and Benditt (264), who found an increase in the alpha-2 globulin fraction in addition to reduced albumin and increased gamma globulin. Bille (25) observed that in clinically mild cases the albumin tended to be normal. Electrophoretic analysis of plasma by the Tiselius technique in several of our cases showed high gamma globulin and fibrinogen concentrations. Smith (239), using a filter paper method, studied the serum protein patterns of 15 consecutive cases from our group. Increase of gamma globulin was present in all, and the albumin was moderately reduced in ten. In six patients with little or no evidence of renal disease the alpha-2 globulin was elevated, but this fraction was reduced in four patients with nephritis and azotemia. In no case was the beta globulin reduced. The pattern in five cases showed a melding of the gamma and beta spots, simulating the pattern often seen in Laennec's cirrhosis. Qualitative abnormalities of the serum proteins in SLE are demonstrable by a variety of tests.

There is no regular association between the L.E. factor and any of the other

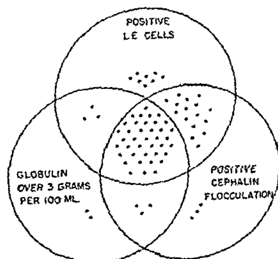


CHART 2 Relationship between hypergl… itive L.E. cell te… tive cephalin-cholesterol flocculation in 76 cases… o cases all three … ga- tive results and would, therefore, be repres… lying outside all

protein abnormalities The relationship between this factor, the total serum globulin and the cephalin flocculation test in 75 of our cases is shown in Chart 2.

b. Sedimentation Rate

Elevation of the erythrocyte sedimentation rate has occurred with great frequency in all of the series of cases in which the results of this test were recorded. Jessar and his associates (129) found an increase in 89 per cent of 245 cases The rapid sedimentation is undoubtedly attributable to the tendency of the red cells to clump, a phenomenon believed to depend on abnormalities of serum globulin together with an increase in fibrinogen The sedimentation rate was determined by the method of Wintrobe in all of our cases, in most on repeated occasions. Very rapid sedimentation was the rule. The value at one hour was often limited by the packing of the red cells and was, thus, largely a function of the hematocrit value Increase in sedimentation was usually observed even though the disease was clinically quiescent However, in eight cases normal rates were observed during periods of active disease. In five of these eight cases the serum globulin was below 3 0 gm. per 100 ml Most of the patients who had normal rates had positive L E cell and cephalin flocculation tests

c. Other Abnormalities

The serum of patients with SLE often gives positive cephalin flocculation and thymol turbidity tests, presumably another evidence of serum protein abnormality. Three-quarters of the patients examined by Jessar (129) had positive cephalin flocculation tests These tests were performed on at least one occasion in 82 of our cases Cephalin flocculation was present in 67 cases There was, in general, good correlation between the results of the two tests Positive tests were often obtained during asymptomatic intervals

Red cell auto-agglutination and the positive Coombs' test sometimes encountered in SLE are attributed to an abnormal serum protein which has the properties of an auto-antibody The circulating anticoagulant demonstrable in the plasma in rare cases of this disease is also thought to be an abnormal protein

Cryoglobulins were demonstrated in the plasma of three of six patients with SLE studied by Barr and his associates (15) The significance of these cold-precipitable proteins is unknown In several of our cases in which hypersensitivity to cold was manifested by Raynaud's phenomenon, cryoglobulins were not detectable

The complement activity of serum is often reduced in SLE Vaughan, Bayles and Favour (262) observed that the degree of depression was roughly correlated with activity of the disease They believed that an apparently reciprocal relationship of complement activity to gamma globulin levels may reflect immune phenomena of importance, and point out that depression of complement activity occurs at the height of antigen-antibody reactions. Elliott and Mathieson (64) measured complement activity in 27 cases of SLE and attempted to correlate the level with other serum protein changes Decreased activity of complement was found in the majority and was associated with albuminuria, decreased serum

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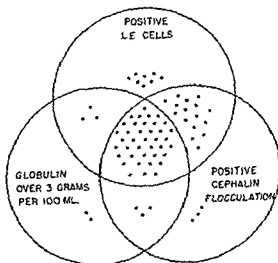


CHART 2 Relationship between hyperglobulinemia, positive L E cell tests, and positive cephalin-cholesterol flocculation in 76 cases of SLE. In two cases all three tests gave negative results and would, therefore, be represented by dots lying outside all of the circles

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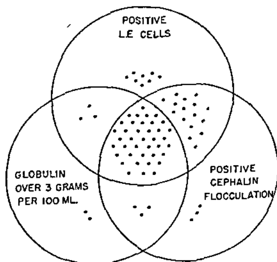
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albumin, increased sedimentation rate, positive or anticomplementary results of complement fixation tests for syphilis, leucopenia and positive L.E. cell tests. Normal values for serum complement were noted in patients with SLE without these associated manifestations. The serum complement activity was not correlated with the concentration of total globulin in serum or with the results of floccul[illegible]

[illegible]

cent the result was positive and doubtful in another 11 per cent. In their opinion, this test has no prognostic significance. Ross and Wells (223) found positive agglutinations in four of seven patients with SLE, but the titers were usually lower than in patients with rheumatoid arthritis. Schleicher (227) has reported a test for "erythrocyte aggregation factor" in the serum of patients with this disease, but others (70) have not found it to be specific or of diagnostic value.

SLE is characterized by striking changes in th[illegible]

[illegible]

constitutes about 40 per cent of each of these mucopolysaccharides and human serum contains definite amounts of bound hexosamine as glucose and galactosamine. Boas and Soffer (27) studied the serum levels of hexosamine in 19 patients with SLE and found that it was increased above the normal range of 85 to 138 mg. % in 17. In 11 patients the levels fell during treatment with ACTH or cortisone, but as the dosage was reduced rose again. The initial fall appeared in from three to seven days. Elevation of hexosamine levels may also be found in other disorders such as leukemia, carcinomatosis, rheumatic fever, periarteritis nodosa, and various chronic infections (28). It may also rise in certain acute illnesses such as pneumonia, myocardial infarction and after trauma. These authors state that at present they cannot interpret their results as relatively little is known of the source, metabolism, and fate of hexosamines or mucoproteins. They are probably related to the depots of mucopolysaccharides throughout the body such as in cartilage, ground substance, blood vessels, and skin.

X. CHRONIC BIOLOGIC FALSE POSITIVE SEROLOGIC TESTS FOR SYPHILIS

a. Incidence in SLE

The occurrence of positive serologic tests for syphilis (STS) in SLE is an observation which led early workers to relate the two diseases etiologically (259). It was soon recognized that these were for the most part biologic false positive (BFP) reactions (77). Coburn and Moore (43) found positive or anticomplementary Wassermann tests in 11 of 30 cases. They stressed the presence of elevated gamma globulin and showed by electrophoretic separations that the substance responsible for positive serologic tests was chiefly in this protein fraction. Many other authors have reported on the incidence of false positive reactions (56, 129, 140, 176, 234). Rein and Kostant (211) examined serum

from 178 patients with various types of lupus erythematosus, subjecting each specimen to a battery of six serologic tests Syphilis had been ruled out as far as possible by history and physical examination. A high percentage of positive results was obtained even in patients with localized discoid lupus.

Zellman (276) studied the incidence of seropositivity in SLE and reviewed some of the pertinent literature. Of 83 cases from the Johns Hopkins Hospital reported by him, 18 per cent were seropositive with standard serologic tests with lipid antigens Of these, one patient was considered to have syphilis, the remaining 14 being possible BFP reactors.

The incidence of seropositivity reported by other workers in SLE ranges from 0 to 44 per cent As Zellman properly emphasized, however, neither his own cases nor any series recorded in the literature could be regarded as accurately representing the incidence of the BFP phenomenon in SLE, since the frequency of occurrence of syphilis in these cases was not determined with certainty.

The Treponemal Immobilization (TPI) Test, devised by Nelson and Mayer (186), is based on the discovery that in syphilitic infection two distinct antibodies appear in the serum: (1) reagin, which reacts with lipid antigens, and (2) an antibody which immobilizes and kills living *T pallidum* The TPI Test is highly specific for syphilis (and other treponematoses), and the immobilizing antibody does not occur in the serum in the absence of treponemal infection. In *untreated* syphilis the TPI Test is approximately 100 per cent positive by the time of and at any time after the secondary outbreak. In *treated early syphilis* the TPI antibody may permanently disappear, though at a slower rate and in fewer cases than does reagin. In *treated late syphilis*, on the contrary, the TPI antibody persists indefinitely and probably for life in at least 97 per cent of cases. These facts make the TPI Test of the utmost importance in the recognition of the BFP phenomenon.

Moore and Mohr (179) point out that BFP reactors are divisible into two groups, which they have designated as acute and chronic. The acute reactions characteristically occur during or immediately following a heterogeneous group of bacterial, viral, plasmodial, or rickettsial infections, and reagin or a reagin-like substance spontaneously disappears from the serum within a period usually not exceeding six months. In the chronic BFP reactors, on the contrary, there is no identifiable precedent acute infection; and reagin persists indefinitely, probably for a life time. The BFP reaction in SLE is of the chronic variety.

In SLE, a positive STS may represent either the chronic BFP phenomenon or concomitant syphilitic infection The incidence of the BFP phenomenon, in series of patients with SLE serologically examined simultaneously with standard and TPI tests, may be expected to vary with three factors: the sensitivity and multiplicity ("battery testing") of the standard serologic techniques employed, the population group, racial and socioeconomic, from which the patients are drawn; and, perhaps, the stages of SLE at which the serologic tests are made.

Standard serologic tests for syphilis were performed in all of our 138 cases

and positive results were obtained on at least one occasion in 38. TPI Tests were carried out in 20 of these 38 cases. The test was not utilized in any STS negative patient; and STS negative-TPI positive concomitant *syphilitic infections* may, therefore, have been missed. The TPI Test was positive in seven patients, who thus had both SLE and syphilis. All seven of these patients were Negroes. Negative results were obtained in 13, who were, therefore, *chronic BFP reactors*. Thus, in the verified SLE patients of our series the incidence of the BFP phenomenon was about 20 per cent.

It has been pointed out (110) that the discovery of the chronic BFP phenomenon may precede any clinical manifestation of SLE by a number of years. This was observed in several of our cases.

b. The Etiologic Background of the Chronic BFP Phenomenon

Pertinent to these observations and proceeding in parallel with this analysis of the clinical features of SLE, is a study of the etiologic background of the chronic BFP phenomenon by Moore and his associates. The discussion which follows is based on a brief preliminary report (180) and on unpublished information (178).

The sole criterion of admission of a patient to this study is his identification as a chronic BFP reactor by means of the TPI Test. About 160 such patients have been so identified, 110 of whom have been carefully studied with long term clinical observations and frequently repeated laboratory tests.

1. Incidence and clinical diagnoses. As to the incidence of the chronic BFP phenomenon these workers have shown that about 40 per cent of white persons of the upper socioeconomic and educational level who are routinely discovered to have a positive STS, in the absence of any history or physical evidence of syphilis and of reasonable opportunity for infection, do not have syphilis and are BFP reactors

In the 110 patients so far analyzed, all are white, 70 per cent females; and the majority in the age group 15 to 35 years. The circumstances that led to discovery of the original positive STS was routine testing of healthy individuals in 62 per cent

Eighty-seven of the identified chronic BFP reactors in this series have been observed for 3 to 20 years. Of these, the present *clinical* diagnoses are:

(a) Six patients have SLE, all verified by the demonstration of L.E. cells Only one of these was clinically recognizable at the time of first discovery of the chronic BFP phenomenon. The remaining five have developed clinical evidences of SLE while under study because of the BFP reaction.

(b) Six patients have rheumatoid arthritis. In two of these (one an 8 year old girl with Still's disease) the arthritis was present at the time of first discovery of the BFP reaction; in the remaining four, arthritis has developed during subsequent observation.

(c) Fifteen had multiple episodes of illness which conform to the clinical pattern of relatively mild and chronic SLE, but in whom the diagnosis has not been verified by the finding of L.E cells. Each of these patients has had at

least two and usually several of the 17 manifestations to be listed below; and the 15 patients have had a total of 58 of these symptoms and/or signs:

Fever, unexplained, usually prolonged and low grade	8 cases
Arthritis and/or significant arthralgia, usually of the hands and fingers	8 cases
Splenomegaly	5 cases
Serositis (pleuritis or pericarditis)	5 cases
Cutaneous lesions (usually discoid LE)	5 cases
Ocular lesions (usually chorioretinal)	5 cases
Raynaud's phenomenon	3 cases
Malaise (noteworthy and prolonged)	3 cases
Phlebothrombosis of major vessels, without obvious cause	3 cases
Psychoses	3 cases
Photosensitivity	2 cases
Mucosal lesions	2 cases
Chorea	2 cases
Thrombocytopenic purpura	1 case
Hematuria	1 case
Convulsions	1 case
Nephritis (this patient died)	1 case

(d) Twenty-two patients have had 55 episodes of illness in which the same group of symptoms and/or signs as those listed above, plus one or two additional ones which may occur in SLE This diagnosis is less convincingly suggested than in the preceding group, primarily because multiple episodes were *less frequent;* and *in none of the 22 have L.E cells been found as yet* The manifestations are, in order of frequency

Arthritis and/or arthralgia	16 cases
Fever, unexplained	10 cases
Malaise, significant	10 cases
Mucocutaneous lesions, bizarre	*6 cases*
Purpura (not thrombocytopenic)	3 cases
Convulsions	3 cases
Psychoses	3 cases
Ocular lesions	2 cases
Nodules	1 case
Paroxysmal auricular tachycardia	1 case
Hepatomegaly	1 case

(e) One patient has Gaucher's disease, with a later superimposed autoimmune hemolytic anemia thought possibly to be due to SLE (not verified).

(f) Five patients have bizarre undiagnosed serious illnesses.

(g) Thirty-two patients are so far clinically normal

2. Laboratory data From the laboratory point of view, these chronic BFP reactors frequently show hematologic changes and disorders of gamma globulin which are likewise commonly present in SLE.

any of the others Anorexia, weight loss, malaise, and fever were commonly present. While fever was usual, several patients with active lupus were afebrile for many weeks.

The development of an infection seemed to serve in several instances as the trigger for enhancement of activity and more rapid progress of SLE. Some patients with latent or chronic SLE were observed to enter a critical phase of activity soon after the acquisition of an infection.

c. The Effect of Pregnancy

In the instances which have been reported pregnancy has had a variable influence on the course of SLE Ellis and Bereston (65) gathered information from their dermatological colleagues concerning the effect of pregnancy on the disease and of the disease on pregnancy. In a number of instances activity of the SLE increased or the mother died, but in many others no change occurred. Spontaneous abortion occasionally resulted. When chronic discoid lesions were the only manifestations there was seldom any change during pregnancy.

In our series pregnancy occurred once in six and twice in five other patients In several instances there was no definite effect of the pregnancy on the course of the disease. In four cases, the initial manifestations developed during the gestation period. Two patients had phlebitis accompanied by fever and malaise soon after delivery, and subsequently developed typical manifestations of SLE. Another, while six months pregnant, had an episode of migratory polyarthritis for the first time. Improvement followed delivery. Two years later she again became pregnant and the joint pains recurred. Once again there was improvement following delivery, but shortly thereafter other manifestations of SLE [illegible] years developed [illegible] nancy, she began [illegible] ing delivery she became free of symptoms, and was well for a period of 16 years. Three weeks prior to admission she became acutely ill with a chill, fever, myositis, polyarthritis, pneumonitis and a cutaneous eruption. L E. cells were found in the peripheral blood Excessive post-partum bleeding led to investigations which established the diagnosis of SLE in one patient. She was a 27-year old Negro female who bled excessively following a tonsillectomy in 1946 In 1949 and again in 1950 there was post-partum hemorrhage requiring transfusions Following the second occurrence, it was discovered that she had a prolonged clotting time, hyperglobulinemia, moderate thrombocytopenia and a positive L.E. cell test.

One patient has been observed during two pregnancies and in both experienced a complete remission, with disappearance of L E. cells from the blood Within four weeks after delivery, there was recurrence of symptoms.

Two patients had a therapeutic abortion performed during the course of active SLE. In one instance this procedure was followed by an acute exacerbation of the underlying disease. In the other the course of the illness was not affected. Spontaneous abortion occurred only once

d. The Cause of Death

Although it is difficult ... was made to det ... patients in whom an autopsy ... true in an illness such as SLE in which one ... organ systems may be involved, and in which the extent of the pathological alterations is hard to evaluate quantitatively

These 38 patients could be divided into two groups: those in whom death appeared attributable to progression of the basic disease and those in whom factors other than SLE appeared to be the cause Twenty-two patients were placed in the first group and 16 in the second.

Group I. All of these patients died during an acute exacerbation of SLE, and during their course showed progressive involvement of one or more organ systems. In five the episode which led to death was precipitated by a drug reaction, in two due to para-aminobenzoic acid and one each to sulfonamide, gold, and streptococcal vaccine

In another five it seemed clear that death was attributable to fulminating SLE; but surprisingly little structural change was found at autopsy, and it was impossible to ascribe death to dysfunction of any particular organ It was, in the words of the pathologist, "as if they had died a "chemical death", leaving behind no structural clues as to its nature"

Three patients died with pulmonary insufficiency, due to typical "lupus pneumonitis" In one of these profuse diarrhea and hemorrhage, resulting from arteritis of the intestinal wall with secondary ulceration, was a contributing factor One patient died with a massive cerebral hemorrhage when a small aneurysm associated with lupus arteritis ruptured A second became comatose following repeated convulsive seizures and died She also developed multiple intestinal ulcerations with bloody diarrhea

Nine patients died with severe impairment of renal function, but in several there were contributing factors In addition to extensive kidney damage, one patient also had alterations of SLE in the brain and lungs Another had obstructive jaundice, generalized bleeding and a terminal *E coli* bacteremia. The third developed subacute bacterial endocarditis on a valve showing the changes described by Libman and Sacks A fourth aspirated a large amount of vomitus during a convulsive seizure and went into profound shock with the subsequent development of acute renal tubular necrosis A fifth was unexpectedly found to have miliary tuberculosis in addition to profound kidney disease caused by SLE A sixth was of interest because a severe renal infection was co-existent with extensive alterations in the kidneys due to SLE The final one had a severe hemolytic anemia complicated by acute renal tubular necrosis

In two patients a severe hemorrhagic tendency, in one with thrombocytopenia, was considered an important factor in causing death The final case in this group was found to have arteriosclerotic heart disease and died with a pulmonary embolus

In addition to the other complicating features already outlined, five patients had a terminal bacterial lobular pneumonia

Group II. The cause of death in the second group was in every instance but one considered to be an infection. This exception was an individual who died in uremia, due to renal arterio- and arteriolosclerosis, the evidence of involvement of the kidneys by SLE being negligible

The frequent occurrence of severe, oftentimes fatal, infection in patients with SLE should be emphasized. Five members of this group had extensive tuberculosis, in two instances with miliary spread, and in two complicated by the development of pneumococcal lobar pneumonia and purulent pericarditis Only one of these five received treatment with ACTH. Two patients had pulmonary abscesses, in one instance due to a pneumococcus, and in the other due to *Pseudomonas aeruginosa*. The latter was accompanied by a fulminant septicemia with focal areas of necrosis scattered throughout the body. A third patient had a huge tubo-ovarian abscess with peritonitis and a beta hemolytic streptococcal bacteremia An acute exacerbation of SLE, terminated by the development of type IV pneumococcal pneumonia with an overwhelming bacteremia, was the cause of death in one. Two patients had widespread urinary tract infection with multiple renal abscesses and *E. coli* bacteremia Another developed a *Salmonella* bacteremia originating from aspiration pneumonia One succumbed to a beta hemolytic streptococcal bacteremia following an acute pharyngitis One patient with extensive renal lesions due to SLE, died of a staphylococcal bacteremia with multiple abscesses in the heart muscle, purulent pericarditis, and abscesses in the brain and kidneys. The final patient in this group died of *Torula* meningitis

XII. THE TREATMENT OF SLE

a Introduction

Although this discussion will be primarily concerned with more specific forms of treatment, it is important to emphasize that many general measures are [illegible] the management of patients with SLE. The control of pain [illegible] algesics, the treatment of complicating [illegible] the use of local applications to reduce the discomfort from cutaneous lesions, transfusions for the correction of anemia, and digitalis and salt restriction in the event of heart failure are examples of numerous therapeutic procedures which should be utilized when indicated. It is our impression that limitation of activity during the active phase of this disease is desirable Undue exposure to the sun is to be avoided, and drugs should not be administered unless definitely needed, in view of the tendency for individuals with SLE to develop allergic reactions.

In view of the protean nature of the clinical manifestations of SLE and the tendency to spontaneous remission, it is difficult to evaluate the effect of treatment A wide variety of therapeutic agents have been tried. These include: salicylates (254), tuberculin (38), gold (16, 195), bismuth (194, 232), arsenic (84), heliotherapy (9, 113), sulfonamides (201, 268), penicillin (181, 247), streptomycin (88, 207), aureomycin (29), chloramphenicol (132), para-aminobenzoic acid (274, 275), nitrogen mustard (58, 200, 219), anti-malarials (47, 86, 142, 191, 226, 243, 269) and vitamin B_{12} (85) With the possible exception of

the salicylates and certain anti-malarial compounds none of these has been demonstrated to have an important beneficial effect.

b. Hormone Therapy

Shortly after Hench and his associates (116) described the effect of cortisone in rheumatoid arthritis, ACTH and cortisone were administered to patients with SLE. Striking clinical improvement was described (63, 89, 100, 252). In most of these early reports treatment was given for brief periods of time, and dosage schedules varied greatly In most instances relapse occurred on discontinuation of therapy, but in some patients the disease remained quiescent for many months

Later, results in larger groups were reported Seven patients, treated by Brunsting and co-workers (33), were given 200 to 300 mg. of cortisone for a few days and then 100 mg daily. The signs of acute disease were promptly relieved, but relapse occurred when the dose was reduced Soffer, Levitt and Baehr (242) reported on 14 critically ill patients, given initially 150 to 200 mg. of cortisone or 100 to 150 units of ACTH daily Subsidence of fever, "toxicity" and joint pain occurred more rapidly with ACTH (12 to 18 hours) than with cortisone (two to four days). Relapse, which occurred in all, appeared sooner upon cessation of ACTH administration (within 24 hours) than after cortisone (five to six days). Leucopenia, thrombocytopenia, abnormal urinary findings and L.E. cells persisted during treatment, suggesting to the authors that the primary disease process was unaltered They stated that the prompt relapses indicated the necessity for prolonged treatment Similar findings were reported by Irons and his colleagues (123). Haserick, Corcoran and Dustan (107) concluded that in desperately ill patients, designated as in "acute lupus crisis", massive doses of cortisone were indicated The treatment consisted of 50 to 100 mg at one- to two-hourly intervals until a response was obtained One patient received 2300 mg. over a 24-hour period

The most comprehensive reports are those of Dubois (59), Soffer and Bader (240), and most recently, Soffer, Elster and Hammerman (241) Certain of their results will be considered subsequently. Shearn and Pirofsky (234) reported beneficial effects in 14 of 20 patients treated with these hormones. Four died during therapy and two others with severe renal impairment succumbed shortly after treatment was discontinued.

Our preliminary results with corticotropin and cortisone over a 12-month period beginning June, 1949 have been described (39). Some patients after single courses of treatment of 14 to 59 days duration entered periods of remission lasting several months During the past three years a wider experience has been gained. Sixty-two of our patients have received ACTH or cortisone In most instances the immediate response has been satisfactory when adequate doses were administered However, cases difficult to control symptomatically even with intensive treatment have been encountered, and a number of patients have required continuation of treatment over long periods Of the 62 patients treated 18 have died

Among the 62 treated patients in our series, the youngest was 13 years; the oldest, 71. Six were adolescents (13 to 19 years) and six were 60 or more years old. The average age among the males (43 years) was slightly higher than that among the females (38 years). These patients had had the disease for periods ranging from one month to 26 years. Forty-six had been ill for at least one year and 26 for at least four.

The clinical diagnosis of SLE was reinforced in 53 of the 62 patients by the demonstration of L.E. cells and in some instances by biopsy.

This analysis covers the period from June 9, 1949, when the first patient was treated, to August 1, 1953. More patients were started on treatment during the first two years of the study (38 patients) than during the last two years (24 patients). The average period of observation in all patients, both living and dead, was 20 months; in the 49 who have survived, 25 months.

The patients with fever were carefully screened for the presence of an infection before treatment was begun. Since the correct diagnosis had not been made, the majority of patients had previously received a wide variety of therapeutic

TABLE XI

Clinical and laboratory manifestations of systemic lupus erythematosus in 62 patients at the start of ACTH or cortisone therapy

Manifestation	Patients
Fever	50
Malaise	54
Arthritis	47
Muco-cutaneous	43
Lymph gland enlargement	34
Pericarditis and/or myocarditis	32
Pleuritis and/or pneumonitis	28
Hepatomegaly	26
Gastro-intestinal	23
Retinal cytoid bodies	18
Splenomegaly	8
Anemia (less than 40% hematocrit)	49
Leucopenia (less than 5000 per mm³)	34
Eosinopenia (less than 100 per mm³)	38 (of 60)
Elevated sedimentation rate (15 mm per hr or higher)	57
L.E. cells	46 (of 53)
Renal abnormalities	
Proteinuria	28
Hematuria	25
Cylindruria	17
Azotemia (NPN greater than 39 mg %)	13
Hypoalbuminemia (less than 3.0 gm %)	19 (of 59)
Hyperglobulinemia (3.0 gm % or higher)	39 (of 58)
Positive cephalin-cholesterol flocculation	42 (of 52)
Thymol turbidity (greater than 5.5 units)	30 (of 54)
Bromsulfalein retention (greater than 10 mg % in 30 min)	8 (of 18)
Biological false positive STS	8

measures Thirty had been given penicillin; 26, one or more of the sulfonamides; 18, one or more courses of gold; and an equal number, salicylates. Smaller numbers had received bismuth, mapharsen, streptomycin, aureomycin, chloromycetin, terramycin or hydroxy-phenyl-cinchoninic acid. With the exception of the salicylates, these agents were of no benefit.

The clinical and laboratory findings in our patients at the time treatment was begun are presented in Table XI

1. Type of treatment. For a number of reasons there has been considerable variation in the treatment schedules of ACTH or cortisone administered. With reference to ACTH, the response to a given dose was not uniform, and the amount that could be safely administered was at times limited by such complications as renal or cardiac disease Early in the study, the dosage schedules were often limited by the available supply. There were frequent changes in the preparations available, purity of compounds, and preferred routes of administration We were seeking the optimal treatment program, and schedules were frequently changed by impressions gained from accumulated experience. The type of hormone, dosage, route of administration, and duration of treatment were determined for each individual by the severity of illness, the physiological functions disturbed, and the patient's response to treatment.

Certain general rules have been applied The patients were in most instances started on dosage levels as follows: 80 to 120 units of lyophylized ACTH intramuscularly daily in four divided doses, 20 to 40 units of the same material intravenously in 5 per cent glucose solution by slow drip over a twelve hour period daily; or 40 to 60 units of highly purified ACTH in gelatin intramuscularly daily in two equal doses. The initial daily dose of cortisone was in most patients 200 to 300 mg, either intramuscularly (once daily or every 12 hours) or orally in four or six divided doses (Table XII).

Each patient was continued on the initial regimen for several days. If there was no beneficial response, the dose was raised in a stepwise manner until a favorable effect was obtained or indications of overdosage appeared. The amount on which clear-cut evidence of improvement appeared was continued until the major signs and symptoms were suppressed to the maximum degree The dose was then reduced in a stepwise manner; that is, by 10 to 20 units ACTH daily

TABLE XII

Initial daily dose, duration of treatment and total dose of ACTH and cortisone administered to 62 patients with SLE

	Initial Daily Dose		Duration (days)		Total Dose	
	Smallest	Largest	Shortest	Longest	Smallest	Largest
ACTH—intramuscular	32 units	140	6	68	318 units	5280
ACTH—intravenous	20	50	8	49	200	1000
Highly-purified ACTH—intramuscular	25	100	7½	37	300	2200
Cortisone—intramuscular	25 mg	400	2	39	500 mg	4115
Cortisone—oral	100	400	3	29	900	4550

Among the 62 treated patients in our series, the youngest was 13 years, the oldest, 71. Six were adolescents (13 to 19 years) and six were 60 or more years old. The average age among the males (43 years) was slightly higher than that among the females (38 years). These patients had had the disease for periods ranging from one month to 26 years Forty-six had been ill for at least one year and 26 for at least four.

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Renal abnormalities	
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Hematuria	25
Cylindruria	17
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[illegible]	42 (of 52)
[illegible]	30 (of 54)
Bromsulfalein retention (greater than 1 0 mg % in 30 min)	8 (of 18)
Biological false positive STS	8

252, 253). Of our 62 patients, 39 had an excellent immediate response to the first course of treatment. In six, however, there was no improvement in the function of one of several vital organ systems. For example, nephritis in two patients remained unchanged although fever and joint pains disappeared, while in another cardiac enlargement and murmurs persisted.

The response in five patients was satisfactory, but proceeded at a slower pace. In eight patients higher daily doses, than those necessary in the majority of our patients (100 units ACTH intramuscularly, 40 units ACTH intravenously or 300 mg. cortisone orally) were required. In six, as the dose was progressively raised improvement occurred rapidly, as though a critical threshold level had been reached

Six patients had little or no response. Four of these after a transient defervescence remained very ill in spite of daily doses of 120 to 140 units lyophylized ACTH, 40 to 60 units of highly-purified ACTH or 300 to 400 mg of cortisone Two died during treatment. In one patient, the chief deficit, thrombocytopenia, was unaffected by 100 to 120 units of ACTH daily for 29 days The sixth received only 1100 mg of cortisone over an eleven-day period

In three patients with renal involvement, treatment was stopped because of hypertension; and in a fourth, who had cerebral manifestations, because of hypertension and drowsiness

The dose was reduced too rapidly in five patients and severe relapses ensued.

In 42 of the 62 patients the course of events after the first period of treatment, during which the patient had improved, was observed. Of the other 20 patients, four died during treatment, four were unaffected by treatment, and ten were continued on treatment at home After a single course of treatment the disease in 15 of these 42 remained quiescent over periods ranging from one to 42 months. The average remission was 12 months, but this is misleading because only five of the 15 patients had remissions of one year or longer, the median duration being six months

Nineteen other patients exhibited the "rebound" phenomenon, described above. The remissions following the rebound lasted from one to 47 months, nine months on the average. This value is also misleading for only four of the 19 had remissions of one year or longer, the median being five months. The rebound began during the period of dose reduction in seven and continued for seven to 17 days In eight patients it began after treatment, as early as one day and as late as ten days; lasting between three and 21 days. In the four others brief relapses occurred during both the dose reduction and immediate post-treatment periods.

In eight patients the relapses following treatment did not subside and the patients continued ill Thus, remissions occurred in 34 of the 42 patients In Table XIII are presented the remissions of one year or longer which have occurred in nine patients following the initial circumscribed course of ACTH or cortisone. A remission denotes either the absence of clinical signs and symptoms or only mild activity. The occurrence of a lasting remission did not seem dependent on the severity of this illness at the time of treatment

intramuscularly or 25 to 50 mg. cortisone every two to four days If there was a recrudescence, the dose was again raised. If, on the other hand, there was no recrudescence or the manifestations were of a minor nature, reduction of the amount of steroid proceeded and treatment was discontinued.

The decision to begin lowering the amount of hormone was based more on clinical manifestations than on the results of laboratory tests. Intensive treatment was not continued because of the persistence of such abnormalities as elevation of the sedimentation rate or serum globulin concentration.

As a result of this method of approach, the total dosage utilized in any single course of treatment varied greatly as did the duration of hormone administration (Table XII) The tabulated values include those for patients who died [illegible] ...d on "maintenance"

[illegible] ...uring the immediate post-treatment period. In those who demonstrated return of activity of the disease treatment was not reinstituted for at least one week unless the patient became very ill. It was observed in several instances that relapse during this first week after therapy was temporary, and a period of essentially complete remission of several months duration ensued. This temporary relapse has been designated as the "rebound phenomenon" (39).

When relapse followed a long remission another course of treatment, usually similar to the first, was given If no lasting remission followed a single course of hormone administration the patient was placed on continuous maintenance therapy. In general, the decision to re-institute treatment has been based on the severity of the recurring features of the disease, the importance of the organ system involved, and the patient's previous response to treatment.

Forty patients were given circumscribed courses of treatment alone without maintenance therapy. Twenty-one had one or more courses of ACTH, and nine patients one or more courses of cortisone. Separate courses of ACTH and cortisone, as many as four, were administered to eight. Of 23 patients placed on maintenance treatment, twelve had previously received circumscribed courses of ACTH or cortisone, whereas in the other eleven maintenance therapy represented extension of the first course of hormone. In all, ACTH was given to 47 patients and cortisone to 38. The total number of courses was 112, of which 25 constituted maintenance treatment.

In all patients, with the exception of a few in whom metabolic studies were being carried out, the intake of sodium chloride was limited to 4 gm. daily or less. In patients with cardiac or renal disease more stringent salt restriction was instituted. Supplementary potassium chloride, 3 to 6 gm. daily, was given to all patients except those with renal disease. Alkalinizing compounds were given between meals. The patients were weighed and the blood pressure recorded daily.

2. Discussion of general results a. THE INITIAL RESPONSE. The rapid and striking improvement in patients with acute SLE given ACTH or cortisone has been repeatedly documented (33, 39, 59, 63, 89, 100, 107, 123, 234, 240, 242,

252, 253). Of our 62 patients, 39 had an excellent immediate response to the first course of treatment. In six, however, there was no improvement in the function of one of several vital organ systems. For example, nephritis in two patients remained unchanged although fever and joint pains disappeared, while in another cardiac enlargement and murmurs persisted.

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Whenever possible the patients remained in hospital during the immediate post-treatment period. In those who demonstrated return of activity of the disease treatment was not reinstituted for at least one week unless the patient became very ill. It was observed in several instances that relapse during this first week after therapy was temporary, and a period of essentially complete remission of several months duration ensued. This temporary relapse has been designated as the "rebound phenomenon" (39).

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RESPONSE The rapid

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TABLE XIII

Clinical remissions longer than one year following initial circumscribed course of ACTH or cortisone

Case History No.	Age, Sex, Color	Treatment						Rebound		Duration of Remission (months)	Subsequent Therapy
		Date begun	Drug	Route	Initial dose (units or mgs)	Days	Total dose (units or mgs)	Occurred	Duration (days)		
H R, 508063	33 MW	July, 1949	A	i m.	75	45	1132	Yes	7	48	No
B S, 510202	43 FW	Aug, 1949	A	i m.	100	38	1780	Yes	3	47	No
H. N, 526560	30 FW	Jan, 1950	C	i m	200	17	2050	No		42	No
O G, 532488	37 FW	Mar, 1950	C	i m.	400	14	2425	No		40	No
G P, 501114	47 MW	June, 1949	A	i m.	100	59	1113	No		34	Yes
S G, 570399	44 FC	May, 1951	A	i v	20	24	385	Yes	3	28	No
R T, 577426	39 FW	Aug, 1951	A	i v.	50	27	838	No		24	No
H T, 415738	40 FW	June, 1952	C	p o	300	20	3050	No		13	No
T M, 579323	50 FW	July, 1951	A	i v	40	29	570	Yes	10	14	No

From our experience there appear to be no significant differences between ACTH and cortisone in regard to remission pattern or the development of the rebound phenomenon. Of 42 patients receiving a course of ACTH initially, 26 had remissions, the median duration being five months, and 16 of the 26 exhibited the rebound phenomenon. Of 15 patients receiving cortisone during the first course, eight had remissions, the median duration being six months, and three of eight exhibited the rebound

b THE OVERALL RESPONSE. On August 1, 1953, 18 of our patients were dead, 42 were alive, and the status of the other two was not known Of the 42 living patients 25 were not on treatment. Nineteen of these were asymptomatic or exhibited mild activity after one or more courses of ACTH or cortisone. Six were seriously ill Seventeen of the 42 living patients were on hormone treatment

Upon reviewing the overall course of events in these 62 patients, several patterns of response emerged (Table XIV).

In nine patients the disease had remained quiescent or mildly active for various periods of time after a single course of treatment. Two of these have had no further treatment during the past four years and two have not been treated for 3½ years Two of these patients were critically ill with evidence of widespread disease at the time treatment was begun. One of these has been at work constantly over these four years [illegible] been relatively asymptomatic. The case history of the other is summ[illegible]

O G. (#532488), a 37 year old white [illegible] critically [illegible] fever, cutaneous lesion[illegible] s, myositis, and p[illegible] 1950 On exam[illegible] high fever ([illegible]

TABLE XIV

Patterns of response to ACTH and cortisone treatment in 62 patients with systemic lupus erythematosus

Pattern of Response	Patients		
Quiescent or mildly active after stopping treatment			16
(a) after one circumscribed course		9	
(b) after multiple courses		4	
(c) after prolonged course		3	
Quiescent or mildly active but on maintenance treatment			11
(a) after long remission following first course		1	
(b) after short remission (s)		4	
(c) after failure to obtain a remission		6	
Progressive active disease			10
(a) in spite of one or more courses		8	
(1) No further treatment because of previous complications	3		
(b) in spite of maintenance treatment from the start		2	
Died			18
(a) after remissions of several months duration		3	
(b) a few months after treatment had been stopped because of complication		4	
(c) shortly after treatment		2	
(d) during treatment		9	
Recent cases satisfactory response			5
Current status not known			2
Total			62

lesions, polyarthritis, subcutaneous nodules, and muscle pain and *tenderness*. The hematocrit was 26% and *increased to* 33% after 1500 ml of whole blood. The *corrected* sedimentation rate was 22–30 mm/hr, and L E cells were *found*

... cortisone 400 mg intramuscularly the first day, 300 mg the second day ... reduction to 100 mg over the next three days ... with an increase to 200 mg again became ... *luction* over the next week At the end of ... joint or chest pain, and the subcutaneous ... two weeks of treatment the hematocrit rose ... s was a reticulocytosis of 3 0% at the end of ... elevated until one week after therapy when

... fully active without symptoms or signs of ... and ankles in the morning or after inactivity ... ocrit was on each occasion 39%; the white cell ... imits L E cells were not seen one, two and

... in a satisfactory state of remission after ... shown signs of ... ctively. The first of these had had active ... es among other manifestations. The nephritis has remained inactive, ... utaneous nodules have recurred

TABLE XV—*Continued*

Manifestations	Author's Series		Soffer and Bader's Series	
	Patients	Effects of therapy	Patients	Effects of therapy
Leucopenia	34	Increase in WBC in great majority, usually within 2 weeks	12	Increase in WBC in 9, no change in 5, reduction in 4
Elevated sedimentation rate	57	Reduced to normal in 29 in 2-3 weeks, improved in 9, persisted in 19	16	Increased in 6, decreased in 5, no change in 7
L E cells	46 (of 53)	Disappeared in only 5 with few cells before therapy	18	Persisted
Renal abnormalities				
Proteinuria	28	Persisted in 14, cleared in 14 along with defervescence		
Hematuria	25	Persisted in 11; reduced in 5, cleared in 9	18	Persisted
Cylindruria	17	Persisted in 9, cleared in 8	14	Persisted
Azotemia	13	Increased in 7, no change in 4 and returned to normal in 2	10	Persisted in 5, returned to normal in 5
Hypoalbuminemia	26 (of 58)	Persisted in 17, improved in 9		
Hyperglobulinemia	39 (of 58)	Reduced in most in 2-3 weeks		
Positive cephalin-cholesterol flocculation	29	Cleared in 12, decreased in 5		
Elevated thymol turbidity	21	Returned to normal in 6, decreased in 6		
Excessive bromsulfalein retention	8	Reduced in all		
False-positive STS	8	Sero-reversal in only 1		

out further treatment One patient developed arthralgia for the first time at the end of her first course of ACTH.

Of 11 patients with joint difficulties who were continued on maintenance doses of cortisone, the arthritis has been controlled by doses ranging from 35 to 200 mg daily.

c MUCO-CUTANEOUS MANIFESTATIONS. Forty-three patients had some form of skin involvement at the start of treatment The site and form of the lesions varied greatly as shown in Table XVI

During treatment the cutaneous lesions cleared completely in 31 patients and incompletely in nine. In two cases there was complete clearing during the first course of treatment, but less improvement with subsequent courses In one case there was no improvement.

There was great variation in the rapidity of response; complete clearing of

TABLE XVI

Effect of ACTH and cortisone therapy on various muco-cutaneous manifestations of systemic lupus erythematosus

Manifestation	Patients	Effects of Therapy
"Butterfly" erythema	15	Cleared within 2 weeks, during 1st week in most
"Butterfly" erythema, scaling and atrophy	16	14 became inactive after 1–4 weeks, during 2nd week in most
Periungual erythema	6	Cleared within 3 weeks
Scattered erythematous macules	7	Cleared within 2 weeks, during 2nd week in most
Extensive erythema and scaling	4	2 cleared after 4 weeks, 2 improved incompletely after 2 weeks
Hyperpigmentation	5	Persisted in all
Focal leucoderma	3	No change in 2, partial repigmentation in 1
Focal subcutaneous swelling	5	Cleared within 1–4 weeks
Subcutaneous nodules	9	Disappeared in 5 after 2–3 weeks
Raynaud's phenomenon	5	Cleared within 1–3 weeks
Alopecia	16	Regrowth of hair in 10, in 4 after therapy
Mucosal lesions, buccal	7	Cleared within 2 weeks

maximal improvement occurred as early as three days or as late as four weeks after start of treatment. Generally, more rapid and more complete healing occurred in patients with lesions of recent onset and those with erythema without edema or scarring.

In 15 patients there was at the end of treatment a recurrence of the type of skin involvement present previously. In most instances it was less severe in degree and in nine the skin cleared in a few days without further therapy.

The cutaneous manifestations usually recurred when the disease became systemically active once again. There was no correlation between the length of the cutaneous remission and any particular type of lesion.

In some instances there was a long cutaneous remission.

Case 37

B. S. (#510202) had had an episode of fever and pleurisy in October, 1948. Three months before admission in August, 1949 she developed maculopapular lesions over the hands which spread to the arms and later extensive lesions appeared over the face and neck. The skin lesions on admission were typical of lupus with erythema and scaling and the diagnosis was confirmed by biopsy. Under ACTH treatment (1790 units intramuscularly over 38 days) healing was complete. After stopping treatment there was a mild relapse which subsided spontaneously. Except for an occasional mild recurrence the skin was essentially normal over the next four years.

Among the patients receiving more than one course of treatment, there was no tendency for greater dissemination of the cutaneous lesions during successive relapses. In only one patient did skin involvement, never previously present, appear after the first course of treatment. One patient after treatment of localized "discoid" dermatitis developed an extensive generalized eruption.

Case 38

J. H. (#186666), a 38-year old colored woman, was admitted in December, 1951 with fever, fatigability, dermatitis, arthralgia, hepatomegaly, anemia, leucopenia and hyperglobulinemia. The cutaneous lesions were restricted to the head, the bridge of the nose and the ears with pruritic, atrophic, and exudative areas. During ACTH, 350 units intravenously over 18 days, the cutaneous lesions became inactive. Six months later the "discoid" lesions became active once again and in addition she developed an intensely pruritic, erythematous maculo-papular eruption over the entire body. She was again given ACTH intravenously, 555 units over 25 days. During the first ten days, both forms of dermatitis became inactive, but the involved areas developed a pitch-black discoloration (Fig. 18). This hyperpigmentation faded appreciably over the next three months.

Six other patients developed prominent brown pigmentation of healing areas during treatment. In patients with long-standing skin involvement it persisted to some degree after treatment. In patients with skin disease of recent onset it disappeared.

In five patients focal subcutaneous swellings, resembling angioneurotic edema, disappeared during treatment. In one case (Case 10), however, the dose



FIG. 18. Case 38. This patient developed intensive pigmentation of the involved areas of the skin during treatment with ACTH.

of ACTH had to be raised to high levels (180 units intramuscularly daily and 60 units intravenously).

Nine patients had subcutaneous nodules, usually near diseased joints These became softer, then smaller, and in five patients disappeared about two weeks after the beginning of therapy.

Raynaud's phenomenon disappeared after one to three weeks of hormone administration in five patients exhibiting it.

Ten of the 16 patients with alopecia had a regrowth of hair, but in four this was not apparent until after therapy. Among the six whose alopecia persisted, treatment was of short duration, interrupted or in low dosage

Seven patients had mucosal lesions all of which disappeared during the first two weeks of treatment.

d. RENAL MANIFESTATIONS. From the early experiences of several investigators (33, 39, 63, 115, 240, 242, 253), it appeared that the renal lesions of SLE were seldom benefited by ACTH or cortisone In patients with renal insufficiency, their administration was often followed by gain in weight, edema, elevation of blood pressure, nitrogen retention, and sometimes pulmonary edema.

Additional experience served to modify this opinion In Dubois' series (59) renal abnormalities, including proteinuria, formed elements in the urine, and nitrogen retention cleared completely in five patients given intensive hormone therapy. In all five, evidence of nephropathy was of recent onset In two others, manifestations indicating renal involvement appeared during cortisone treatment and disappeared after the dose was raised. Haserick (107) noted decrease in proteinuria and hematuria in several patients given large doses of cortisone Soffer and Bader (240) reported that hematuria and cylindruria persisted in spite of vigorous treatment, but in five of ten patients with azotemia the blood urea nitrogen returned to normal levels coincident with defervescence and rehydration.

Thirty-six of our 62 patients exhibited one or more renal abnormalities before treatment. Twenty-eight had proteinuria In 14 of these no dramatic change occurred during therapy In the other 14 the proteinuria cleared completely, but in most instances it was probably associated with the febrile state and not due to involvement of the kidneys by SLE.

Twenty-five patients had hematuria which was microscopic in all but three No change occurred in 11 patients, in five there was an appreciable reduction; and in nine, the hematuria cleared during treatment. However, in seven of these nine the hematuria was minimal in degree

Casts were noted in the urine of 17 patients before treatment. In six, these persisted during treatment; in three, they disappeared during some courses, persisted in others; and in eight patients they cleared completely.

In 13 patients the non-protein-nitrogen (NPN) concentration in the blood before treatment was elevated (greater than 39 mg. per 100 ml.). During treatment the NPN fell to within normal limits in two, increased slightly in four; and increased appreciably (between 22 and 143 mg per 100 ml.) in seven.

In 12 patients with renal insufficiency there was no improvement in kidney

function in five; in six, treatment was stopped or the dose rapidly reduced because of sudden elevations of blood pressure, body weight or non-protein-nitrogen concentration. The most favorable response is described in the following report:

Case 39

H D (#575863), a 50-year old white male foreman, had been well until January, 1950 when he developed generalized muscle pains and polyarthritis In November, 1950 an 18-day course of cortisone resulted in improvement, but immediately after withdrawal the arthritis returned He was then placed on maintenance cortisone, 100 mg. daily being required for relief Four months later he suddenly had severe weakness and headache thought due to "cortisone reaction" Cortisone was discontinued and gold started in March, 1951. After a few injections he developed blurred vision, periorbital edema and severe weakness Gold therapy was stopped and after BAL administration vision returned. Soon thereafter he developed hypertension, anemia, leucopenia, proteinuria, hematuria and cylindruria. On admission in June, 1951 he appeared chronically ill with muscle atrophy and weakness, arthritis, subcutaneous nodules, retinal cytoid bodies, cardiomegaly and blood pressures of 160–175/90–110 mm Hg Urinalysis revealed proteinuria (++++); 10-15 red cells, 5-10 white cells, 2–6 hyaline and granular casts per high-power field. Maximal specific gravity of the urine was 1 017 Phenolsulfonphthalein excretion was 45% in two hours. NPN was 48 mg %; serum albumin 1.8 gm % Muscle biopsy revealed perivascular inflammation and atrophy L E cells were found On July 3, 1951, a 28-day course of intravenous ACTH was begun Muscle weakness, arthralgia, subcutaneous nodules, and cytoid bodies disappeared The blood pressure fell slowly to 140/90 mm and heart size returned to normal Proteinuria was reduced to one plus and there were fewer formed elements in the urinary sediment PSP excretion increased to 66% in two hours. NPN rose rapidly to 60 mg % during the first week then fell to 36 mg % during the third week The serum albumin increased to 2 5 gm % during treatment and to 4 2 gm seven weeks later Ankle edema disappeared during treatment, and there was loss of six pounds in weight

Eleven weeks after discharge he was readmitted with myositis, arthritis, subcutaneous nodules and lymphadenopathy. The blood pressure was 105/70 mm Hg. Urinalysis showed only a trace of albumin, and there was concentration to 1 027. NPN was 36 mg % and the serum albumin, 3 4 gm % PSP excretion, however, was 40% in two hours During a 16-day course of ACTH there was again striking improvement The PSP excretion rose to 82% on the 6th treatment day and the serum albumin to 4 6 gm % Over the next 21 months the patient was virtually asymptomatic and at work, the urinalysis, NPN and serum albumin remained normal, but the PSP excretion fell gradually to 56% in two hours

e. CARDIAC MANIFESTATIONS. Eighteen of our patients showed evidence of pericardial disease at the start of therapy. Only one had a massive effusion and this was unaltered Five of 18 with pericarditis also had renal involvement with azotemia. In three of these there was no change during treatment in either renal or pericardial disease. In one receiving a maximum of 100 mg. cortisone daily, there was further cardiac enlargement and a pericardial rub appeared. In one patient all evidence of pericarditis (substernal aching, friction rub, cardiac enlargement and peripheral edema) cleared within the first week.

Of the 13 patients with pericardial but no renal disease, there was no change in six, further cardiac enlargement in one, and improvement in six after one to two weeks of therapy Peripheral edema, present in three, disappeared by the end of the second week. A patient with normal cardiac findings before treat-

ment developed a pericardial effusion after two years on maintenance cortisone treatment, 50 mg. daily.

Seventeen had evidence of myocardial involvement at the beginning of treatment In the eight patients who also had renal disease, the results of therapy were variable: no change in five, a gallop rhythm developed in one and in two the heart size became normal after three weeks coincident with improvement in renal function.

On the other hand, eight of the nine patients with myocarditis but good renal function improved during treatment In three desperately ill patients in severe cardiac failure, the response was dramatic. Cyanosis, substernal pain, orthopnea, gallop rhythm, palpitations and peripheral edema cleared by the end of the second week; cardiac enlargement decreased; and the patients were up and about the ward by the end of the third week of therapy. Two have been continued on cortisone and the improvement maintained Treatment was abruptly stopped in the third after reactivation of a duodenal ulcer Continuation of digitalis and sodium restriction has not been entirely satisfactory and the heart has become larger and orthopnea has reappeared.

Two patients not considered to have myocardial disease on clinical grounds developed heart failure while receiving ACTH and at autopsy extensive "lupus myocarditis" was found

There was no significant effect of treatment on cardiac murmurs in any case.

f PULMONARY MANIFESTATIONS Pleuritic pain, present in 15 patients, disappeared as early as the third day of treatment, usually within the first week, but in two instances not for three weeks Eight of the 15 had pleural changes on x-ray, in four, there was a definite effusion These changes cleared after one to three weeks of therapy in seven

Of nine other patients with both pleural changes and focal atelectatic pneumonitis at one or both lung bases, two showed complete clearing during treatment; four, almost complete clearing, and three, clearing during some courses and no change during others Maximum improvement usually did not occur until the third week. The following case illustrates healing of pulmonary manifestations during treatment followed by a long remission

Case 40

G P (501114), a 47-year old white businessman, had had constant fever and arthritis for 11 months and progressive dyspnea for three months before ACTH therapy was started on June 9, 1949 At this time, atelectatic rales were heard at both lung bases and chest x-ray revealed disc-like areas of atelectasis at both bases (Fig 13) Within 24 hours after starting treatment fever and arthritis disappeared, and the sedimentation rate was normal on the fourth day Dyspnea was relieved and rales had vanished by the end of the second week. The chest x-ray, taken at the end of his 59-day course of ACTH, revealed considerable improvement He remained symptom free and at work over the next 34 months after which hormone therapy was resumed because of the appearance of microscopic hematuria

g. GASTROINTESTINAL MANIFESTATIONS Symptoms referable to the alimentary tract were present in 23 patients at the start of hormone therapy. Some complained of the difficulty in swallowing A sore, swollen red tongue was

the cause in one and abated under cortisone. Three patients had prompt regurgitation of food after eating but in only one did x-ray studies reveal esophageal disease (Fig 14 A) During a brief course of ACTH given to this last patient there was no improvement. In the other three patients regurgitation of food ceased promptly after the start of treatment.

Seven patients complained of crampy abdominal pain which was generalized in one instance and epigastric in six. In four no basis other than SLE was found. During treatment the pain slowly subsided and was gone at the end of two weeks in three The pain continued in the fourth, but she received only 100 mg. of cortisone daily. One patient had less epigastric distress during treatment, but it persisted She was jaundiced, and this was uninfluenced by treatment. Two patients had epigastric distress suggestive of peptic ulceration. One had had a slight deformity of the duodenal bulb roentgenologically. The pain subsided during the first week but at the end of treatment she developed fever, acute generalized abdominal pain, tenderness and distention. It was suspected that an ulcer had perforated, but the pain spontaneously disappeared within 24 hours, although the fever continued for two weeks In the other patient the pain subsided during the first week of therapy but recurred. She developed hematemesis and at necropsy an acute gastric ulcer was found.

Nausea and vomiting were prominent manifestations on admission in 13 patients. In all instances these cleared during treatment. One patient developed melena during treatment and at autopsy there were many ileal ulcers. It is possible that impaired fibroblastic activity secondary to ACTH administration may have impeded healing of the ulcerations.

h. LIVER AND SPLEEN. In the 15 patients with hepatomegaly in whom liver size was closely observed during treatment this organ became progressively smaller in all but one. In 12 the liver edge was not palpable after one to four weeks.

Evidence of hepatic dysfunction as reflected by excessive bromsulfalein retention before treatment was present in five of 16 patients. In two, there was less retention during treatment, from 3.0 to 1.1 and 1.9 to 0.7 mg. per 100 ml., respectively In the other three, only slight reductions occurred.

One patient had a serum bilirubin of 3.5 mg.% and alkaline phosphatase activity of 82 Bodansky units. During treatment, which never exceeded 100 mg cortisone daily, the hyperbilirubinemia disappeared and the alkaline phosphatase activity gradually fell to 20.9 units, only to rise to 58 0 units shortly before death. The liver was not palpable and the cephalin flocculation and thymol turbidity tests were normal. At post-mortem examination the liver was studded with miliary tubercles.

Cardiac abnormalities were noted in nine of the 12 patients in whom hepatomegaly disappeared during treatment. In five the heart was significantly enlarged by x-ray and in three patients in whom it was measured the venous pressure was elevated. During treatment, heart size returned to normal in two of the five and venous pressure to within normal limits in all three patients

The spleen was readily felt in only eight patients before treatment The

splenomegaly subsided within the first week in seven and after three weeks of therapy in the other who had the greatest enlargement noted.

i. LYMPH NODES In all but three of 34 patients with lymphadenopathy the nodes could no longer be felt after three days to three weeks of hormone administration In more than one-half of the patients they were not palpable by the end of the first week of treatment These changes were particularly impressive in the following patient:

Case 41

H. F (#527492), a 40-year old white woman, had had attacks of urticaria and angioneurotic edema for many years Two months before treatment she developed fever and generalized lymph node enlargement On admission in February, 1950 the nodes, particularly in the neck, were so large and tender that the initial diagnoses considered included Hodgkin's disease, infectious mononucleosis and tuberculous adenitis Lymph node biopsy (Fig 3) showed focal areas of necrosis, and L E cells were found in the peripheral blood She was given ACTH, 100 units daily intramuscularly On the third day she was afebrile and only one small supraclavicular lymph node could be felt She received a total of 835 units of ACTH over 15 days A second lymph node biopsy obtained on the seventh treatment day revealed changes which were similar to, but much less prominent than, those seen in the first specimen. She was well for five months at which time cervical adenopathy reappeared On ACTH she again improved rapidly and had a remission of four months duration Subsequently, she was given cortisone intermittently When last examined in February, 1953 she was taking 50 mg of cortisone daily and there was no lymph node enlargement

Two of the three patients whose lymph nodes remained large had a satisfactory response to treatment in other respects In the third the nodes were calcified, probably due to tuberculosis

At the end of treatment lymphadenopathy reappeared transiently in seven patients.

j. RETINAL LESIONS No consistent effect on the cytoid bodies was observed during ACTH or cortisone therapy in 18 patients

k. HEMATOLOGICAL MANIFESTATIONS *Red cells* At the time of treatment, 49 of our 62 patients had some degree of anemia (hematocrit less than 40%) which was in most instances normochromic and normocytic

Of the 34 patients with moderate or severe anemia, i e hematocrit values below 35%, 17 improved during treatment with hematocrit elevations averaging eight units. Moreover, nine of the 17 patients gained seven to 16 pounds in weight during this period. The hematocrit rise usually began at the end of the first week, but in 15 did not reach its maximum for three weeks or more. Of 12 improved patients followed, five had further increases during the post-treatment period, five maintained improvement and in two the hematocrit returned to pre-treatment levels within two weeks

In six patients with progressive azotemia the anemia grew worse.

In the other 11 anemic patients no rise in hematocrit followed hormone therapy. Seven, however, were followed for no longer than two weeks.

White cells In 34 of our treated patients the white cell count was below 5000 per mm.^{3}, in 23 it was normal, and in five above 10,000.

Of the 34 with leucopenia before therapy two had a further reduction in the

count, 1500 to 1800 per mm.³, respectively. In the other 32, increases of 200 to 12,000 per mm.³ took place; the average being 4,800. This occurred between three days and five weeks after beginning treatment, the average being two weeks. The following case illustrates the effect of treatment in a patient with severe leucopenia:

Case 42

J. F. (#636867), an 18-year old white girl, had had an extensive facial rash for one month and fever, anorexia, malaise and muscle aching for two weeks. On admission she was anemic and the white count was 500–1200 per mm³ She received a 29-day course of H P. Acthar-gel [illegible] treatment, the white cell count was 6,100.

In the patients with a normal white count before therapy, increases occurred with the same frequency and were of the same magnitude.

Of the five patients with leucocytosis before treatment, two had tuberculosis There was no apparent infection in the other three. During treatment the white count decreased in two and increased appreciably in the other three.

The largest cellular increments occurred precipitously in a patient who developed a staphylococcal septicemia during ACTH treatment; a patient with widespread tuberculosis, and another who developed a Cryptococcal meningitis. These examples serve to emphasize that when a sudden leucocytosis occurs the physician should suspect a complicating infection.

Eosinophils. The eosinophil count in patients with SLE tends to be low During treatment the count fell to zero in 34 of 61 patients. No change occurred in five whose initial counts were low and in three patients the eosinophils became more numerous during treatment.

After hormone administration was stopped the counts returned to pre-treatment values in most instances. In eight patients, whose counts were low, they rose to within the normal range after therapy.

The L.E. cell phenomenon. Dubois (59) noted the complete disappearance of L.E. cells in some patients within six weeks after the induction of a remission by ACTH or cortisone He postulated a direct correlation between the number of cells and evidence of activity of disease, especially fever. Haserick (107) observed the disappearance of L.E. cells in five of 16 treated patients and Shearn and Pirofsky (234), in four of 20. Soffer and Bader (240), on the other hand, reported that L.E. cells persisted during both drug-induced and spontaneous remissions.

The effects of ACTH or cortisone on the L.E phenomenon were observed in 21 of our patients. In five the abnormal cells disappeared during treatment, but in each instance they were described as "rare" before treatment. In eight they became less numerous and in six no change occurred. In two patients a few more cells were seen during hormone administration than before

After prolonged hormone treatment the L E. cells became less numerous, but were still present in four patients. In another, however, in whom L.E cells had

been seen in moderate numbers before, only one was seen after seven months on cortisone, but after a second seven months they were found in abundance.

There was no correlation between the persistence of L.E. cells and the completeness of the clinical remission.

l. OTHER PROTEIN ABNORMALITIES. The serologic test for syphilis. At the time of treatment, 11 patients had positive serologic tests. The TPI Test was negative in eight of these. During hormone administration the serologic test became negative in only one patient

The positive STS in the other three patients, all colored females, were presumably due to syphilis on the basis of a positive TPI Test in all three after penicillin therapy. No significant change in these serologic tests occurred during hormone therapy.

Sedimentation rate. In 57 patients the corrected sedimentation rate was elevated. The range was 16 to 47 mm./hr , the mean, 30 and in 30 patients it was 30 or higher. The sedimentation rate fell during therapy to less than 15 in 29 of the 57 patients, to less than 10 in 17. In nine the rate was reduced by at least 10 but was never less than 15 No significant change occurred in 13 patients

The return to normal levels took place from three days to six weeks after starting the hormone; the average time being 17 days Of the 15 patients in whom the rate fell to normal and was measured during the first two weeks after treatment, it returned in all to elevated values In only one of these did it then fall to within normal limits without further therapy. There was no direct correlation between the dose of hormone and the degree of reduction of sedimentation rate. Moreover, changes in the rate during treatment did not correlate well with changes in serum globulin concentration, cephalin flocculation or thymol turbidity.

When the sedimentation rate returned to normal there was always a satisfactory clinical remission. However, in many instances the patient had a good remission from the clinical point of view while the rate remained elevated.

Serum proteins and liver function tests In Soffer and Bader's series (240), 15 of 18 patients had a low serum albumin, which during therapy increased in nine, was unaltered in three, and decreased in three The serum globulin was high in 16 patients and with therapy there was a reduction in ten, no change in two and an increase in four. From serial electrophoretic patterns Reiner (212) [illegible]

depression of gamma globulin during treatment and coincident with this a rise in the non-specific complement titer. Similar changes were also observed by Carey (39).

Thirty of our patients at the time of treatment had serum albumin concentrations lower than 3 0 gm. per 100 ml. With therapy there were increases in nine of 0.7–1.8 gm., averaging 1.1; an increase during some courses of hormone administration and no change during others in two patients; no change in fifteen; and in four serial determinations are not available Of the fifteen patients

in whom no change occurred, ten had proteinuria, and two had hepatic disease Of twenty-four with serum albumin concentrations of 3.5 gm. or higher there were increases in six of 0 6–1.2 gm., averaging 0 8, varying responses during different courses in two; and no change in sixteen. Maximal elevation of the albumin did not occur until the end of the second or more frequently the third week.

Of the thirty-nine patients with serum globulin concentrations of 3 0 or more gm. per 100 ml. at the start of treatment, there were reductions in twenty-five of 0 6–2 8 gm , averaging 1.3; variable responses in three; no change in five, and no subsequent determinations in six. Furthermore, seven of twelve with globulin concentrations of 2 5–2.9 had reductions of 0 6–1.2 gm., the average being 0.9. In general, the change was greater in those with the higher initial concentrations and was not maximal until the second or third week of therapy. Of twenty-nine patients with positive cephalin-cholesterol flocculation before treatment, the test became negative in twelve It was less positive in five, the response was variable in two, there was no change in eight, and more flocculation developed in one during an allergic reaction to ACTH. All but one of the twelve in whom the flocculation disappeared during therapy had a concomitant fall in serum globulin.

The thymol turbidity was elevated, greater than 5 5 units, at the start of hormone administration in twenty-one patients in whom serial observations were made. It returned to normal in six, was reduced in six, improved during one course and was unchanged during another course in two, was unchanged in six and increased in the patient with ACTH hypersensitivity.

In most patients various protein abnormalities recurred promptly after treatment was discontinued.

4. Some generalizations concerning hormone therapy. We have been particularly concerned with the criteria of adequacy of treatment. As previously stated, there was at the beginning an attempt to revert all abnormalities, including those indicated by laboratory tests, to normal We found, however, that in several patients who became asymptomatic during hormone therapy, and had no signs of active SLE except a persistent elevation of the sedimentation rate, positive STS and L E. cells, continuation of treatment for one or two weeks longer resulted in no further improvement. Dubois (59) believed that "the obvi- [illegible] than stereotyped dosage
[illegible] termine the effectiveness
[illegible] of our patients have en-
[illegible] thout the induction of a
Cushing's state, even with the most liberal definition of this condition. What is really needed is a reliable index of disease activity which is currently not available.

Even more perplexing is the evaluation and desirability of long-term treatment with these hormones. Does treatment, no matter what the details of administration, influence the overall course of the disease? Is continuous treatment, which has now been adopted by most groups of investigators su-

perior or inferior to intermittent courses of treatment, which we have used in many of our patients? Because of the chronic and relapsing course of the disease and the variable results of treatment, answers to these questions will only be realized through observations over long periods of time. Analyzing the results of treatment in patients, year by year after the discovery of the L.E. cell, Haserick believed that mortality had been reduced by hormone administration (101). Dubois recommended continuous treatment and stated that such treatment had prolonged life. However, whereas the incidence of spontaneous remissions in his untreated patients during the 15 years prior to 1950 was 20 to 40 per cent, only two of 21 patients in the continuous treatment group maintained their remission when treatment was stopped. He concluded from statistically inconclusive data that "the frequency of occurrence of spontaneous remissions seems to be lowered by therapy" and it is suggested that "milder cases be observed during a rest period of several weeks prior to starting treatment". This has been our practice both before initial treatment and after therapy when exacerbation following a remission has taken place. However, what constitutes sufficient activity for treatment or retreatment is difficult to ascertain. Generally, this is determined by the severity of symptoms and signs of activity as well as the importance of the organs involved. It is possible that continuous treatment may prevent or minimize further damage in a vital organ in which some irreversible alteration has already occurred.

In our experience there is little, if any, difference between the suppressive effects obtained with ACTH and those with cortisone. There may be less danger of adrenocortical insufficiency after a course of ACTH, but oral cortisone is easier to administer. Cortisone produces less salt retention and is usually preferable in patients with cardiac or renal disease. With cortisone one does not run the risk of inducing an allergic reaction. However, these are unusual with currently available preparations of ACTH.

These hormones do not constitute a specific treatment for the basic disease. However, as Soffer and Bader (240) stated: "Despite the risks attendant on the use of these hormones, they constitute the most effective agents yet available for the treatment of this disease. It must be emphasized, however, that no cures result. It is possible that some patients may be maintained in a state of remission for an indefinitely prolonged period of time with judicious treatment". With this we concur. More effective therapy may be expected to result from a clearer understanding of the pathogenesis of the disease. However, until that time, we would feel that ACTH or cortisone treatment is indicated in most patients with clinically active SLE.

5. Complications of hormone therapy. In patients with SLE the manifestations of the disease and the complications resulting from treatment with ACTH or cortisone may simulate one another. Such complications as heart failure or convulsions may develop either as a consequence of active SLE or as a "side-reaction" to hormone administration. These various complications are summarized in Table XVII.

Approximately one-half of our patients (32 of 62) developed some type of

TABLE XVII

Complications of steroid therapy in systemic lupus erythematosus: hormone- or disease-induced

Complication	Patients	Complication	Patients
Patients treated	62	*Infection*	20
Cardiovascular	32	Focal only	15
Excessive weight gain (7+ lb)	20	Systemic	5
Manifest edema	11	Gastrointestinal	12
Congestive heart failure	2	Abdominal pain	8
Hypertension	16	Diarrhea	4
Nervous system	31	Hypersensitivity	11
Restlessness	12	ACTH most likely	6
Psychosis	10	Other agents	5
Euphoria	7	Thrombophlebitis	5
Depression	5	Amenorrhea	4
Convulsions	5		
Paresthesias	3		
Confusion only	1		
Paranoia, mild	1		

cardiovascular complication. Twenty gained an excessive amount of weight ranging between 7 and 22 pounds, the average being 13. In 12 of these there was no evidence of cardiac or renal disease, and in two no salt restriction had been instituted

Two patients developed congestive heart failure which responded to further salt restriction and digitalization without drastic reduction in ACTH dosage.

Significant elevation of blood pressure occurred during therapy in 17 patients Of the nine with normal blood pressure at onset of treatment, three had renal disease, and of the eight with hypertension four had renal disease. The blood pressure elevations in all seven with renal involvement occurred so abruptly and were accompanied by such rapid accumulations of fluids that in five it was thought advisable to stop the hormone.

The presence of cardiovascular-renal disease, however, is not an absolute contraindication to hormone therapy. In contrast to seven patients with cardiac disease who gained an average of 13 pounds during treatment, there were seven others who diuresed, losing between eight and 27 pounds. In most of these latter cases the cardiac manifestations were probably due to SLE. In such patients the salt intake was restricted to a maximum of 0 5 gm. daily and cortisone was administered at full dosage. The patient was usually digitalized and if fluid retention developed diuretics were used.

Convulsive seizures and behavior disturbances of various types occur during [illegible] during hor- [illegible] when [illegible] ermine [illegible] is (56) [illegible] after the [illegible]

recent exacerbation of the illness, is febrile, normotensive and without recent weight gain. In our experience these features are not always sharply defined.

The most common nervous system manifestation among our treated patients was hyperirritability which occurred in 12. This was variously described as feeling "nervous", "restless", "jumpy", "shaky inside" or having "a funny feeling in the head". It occurred only in patients receiving large doses of hormone.

Nine patients became psychotic during treatment. Another became psychotic two weeks after an 11-day course of cortisone during which no improvement had taken place. All these reactions took the form of severe paranoid delusions. Of these ten patients three had had similar psychotic episodes before hormone administration. Such an episode during hormone therapy was the prelude to convulsions in two patients. In two others the abnormal behavior appeared in relation to an acute flare-up of SLE coincident with the development of hypersensitivity to ACTH.

Ransohoff and co-workers (206) noted rapid clearing of a psychosis in a patient given potassium intravenously In none of our patients was the serum potassium concentration low during the abnormal behavior nor did the administration of potassium intravenously have any immediate effect

That ACTH and cortisone may play a significant role is supported by the rapidity with which the psychosis cleared after treatment was discontinued In most patients the reaction disappeared within one week, the longest period being one month However, in one, cortisone was continued because of high fever, and the psychosis cleared after ten days

A mild euphoria appeared in most patients after the initial symptomatic relief induced by therapy. However, in seven it was greater in degree than would be expected to result from elation over improvement in the basic disease On the other hand, five patients became depressed In two this was pre-terminal The other three were relatively resistant to treatment, requiring high doses of hormone over a period of several weeks.

ACTH and cortisone have been reported to induce status epilepticus, unusually resistant to anti-convulsive therapy, in patients with asthma, acute rheumatic fever, periarteritis nodosa and dermatomyositis (54, 161) The frequency with which convulsive seizures appear during the course of SLE, especially preterminally, has been discussed The differential diagnostic features outlined by Dubois (56) may be helpful if the clinical picture at the time of the convulsions clearly falls into one of his two groups which it often does not. Russell and his colleagues (224) noted improvement during ACTH and cortisone administration in two patients who had had repeated epileptiform seizures of several years duration. However, in three patients in whom the convulsions were associated with acute fulminating SLE, cortisone seemed to exert no effect. In two patients abnormal electroencephalographic patterns disappeared during treatment. In Dubois' series of 22 patients with seizures, 19 were thought to be due to disease and three to treatment.

Only five of our patients had grand-mal seizures Of these, two had convulsions when not on treatment, and the other three were preterminal with ful-

minating SLE, one in advanced uremia. All five had active nephritis and four had fluid retention and hypertension. Convulsions did not appear in any of several patients receiving very large doses of hormone. In our experience convulsions occuring during treatment are likely to be the result of active disease, but if there has not been adequate restriction of sodium intake during intensive therapy, the hormones certainly may play a role There is no convincing evidence that hormone administration can significantly alter the convulsive state due to active SLE. Seven of 12 patients studied in our series had abnormally slow electroencephalographic patterns before treatment and one had low voltage as well. Five of these had serial records and in three the tracings became normal during therapy; in one, less abnormal, and no change took place in the other.

There is evidence to support the concept that ACTH or cortisone may inhibit the host's ability to cope with infectious agents. In the first 662 courses of ACTH given in this hospital 13 generalized infections developed. In almost every instance, however, the patient had an illness, such as a blood dyscrasia, a severe burn, severe ulcerative colitis or a connective tissue disease, in which the predisposition to a superimposed infection was high. All patients should be investigated for infection before instituting hormone therapy. Moreover, any patient in whom fever recurs during ACTH or cortisone administration should be considered to have an infection until proven otherwise. Among our treated patients 20 developed one or more localized infections during therapy. The most common site was the urinary tract (six). In two patients pre-treatment urinary tract infections became more severe during ACTH administration Paronychiae appeared in three patients during treatment, two had the characteristic periungual erythema of lupus and had had similar episodes previously. Two with alopecia developed staphylococcal scalp infections. One of these was particularly prone to infections for during three courses of treatment she developed, in addition to the scalp infection, a cellulitis of the face, axillary impetigo, and a lung abscess with a *Pseudomonas aeruginosa* bacteremia. An abscess on the buttock at an ACTH injection site appeared in one patient. One developed an acute sinusitis and another oral moniliasis.

Generalized infections developed in three patients and tuberculosis was made worse in two others One was the patient with the *Pseudomonas* bacteremia probably arising from a lung abscess Cryptococcal meningitis was the cause of death in another. One had two episodes of staphylococcal septicemia from a focus in the urinary tract.

There are several isolated case reports of either the appearance of miliary tuberculosis following hormone therapy in patients with SLE (51, 99, 263) or the reactivation with lymphatic spread of an old, healed tuberculous lesion (203).

Soffer and Bader (240) gave each of their 18 patients a routine trial on an antibiotic before starting treatment and reported no complicating infections. We have not elected to use prophylactic chemotherapy because it may interfere with the detection of an infection, and also because of the high incidence of drug reactions in patients with this disease.

Eight of our patients experienced abdominal pain during treatment Three had mild to moderate epigastric discomfort which responded readily to antacids. One who had a known duodenal ulcer, developed melena and anemia. One patient, while on low doses of cortisone, developed hematemesis and melena, shown to be due to an acute gastric ulcer.

Six patients had allergic reactions thought to be due to ACTH (236). These occurred during the first course of treatment in five of the six; during the third course in the other. In two the animal source of the hormone was the pig; in one, the sheep, and in three, a mixture of pig, sheep and cattle. It is of interest that, as with other sensitizing agents, reactions to ACTH have been more numerous in patients with SLE than in other disease groups In this hospital 11 ACTH reactions have been observed among more than 1000 patients given this hormone and six of these occurred in the 62 patients with SLE

c. *Other Measures*

Aside from the usual supportive measures other agents have been used in patients with SLE Only a few merit brief discussion.

1. *Acetylsalicylic acid* (*ASA*). Perhaps the most useful drug other than the hormones in the management of SLE is ASA In many instances there is rapid defervescence (Chart 3) and the patient feels greatly improved, as in the following case·

Case 45

S D (#608952), a 21-year old white female, was admitted in June, 1952 with a three-year history of episodes of fever, chilly sensations, weight loss, butterfly erythema, migratory polyarthritis and pleuritic pain. She had received several courses of ASA or cortisone, each of which had induced partial symptomatic relief On admission the temperature ranged

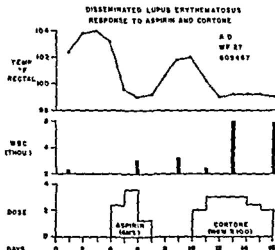


CHART 3 Comparative effects of acetylsalicylic acid and cortisone on the fever and white cell count in a patient with SLE

between 102° and 104°F. The elbows could not be fully extended. There was a "butterfly" eruption and erythema over the neck Subcutaneous nodules were felt in the occipital region and there was generalized lymphadenopathy One cytoid body was seen. Laboratory abnormalities included anemia, leucopenia, elevated sedimentation rate, hyperglobulinemia, positive cephalin flocculation, and L E cells in the peripheral blood.

On the fourth hospital day, after a single dose of 0 6 gm. of ASA the temperature fell from 103 8°F. to 97.6°F. within four hours and she felt better Over the next week ASA was continued at 2 4 gm daily She remained afebrile and the occipital nodules disappeared. However, nausea and joint pains continued and the aspirin was stopped. Two days later the temperature rose to 104.8°F , occipital nodules reappeared, nausea increased and vomiting ensued H P Acthar-gel, 40 units daily, was started Defervescence was slower than with ASA, but on the second treatment day, although the temperature was still 101°F , she felt better than on the second day on ASA with no nausea, good appetite and no joint pain

Such a rapid defervescence following the administration of ASA does not always occur. Of 19 patients in whom there was adequate documentation of treatment with this drug, eight had no response, even with as much as 6 0 gm. daily. Four patients experienced a prompt remission of fever but joint pains persisted and conversely, in one patient joint pains were controlled but fever continued.

In the six other patients striking responses, similar to those which occurred in the patient whose case history was described above, took place. Four had

of atabrine (quinacrine hydrochloride) in most patients with chronic discoid lupus erythematosus, has now been repeatedly confirmed (47, 142, 226, 243, 269). His treatment schedule consisted of 100 mg. three times daily for the first week, 100 mg twice daily for the second week; and then 100 mg. daily. Kierland and co-workers (142) point out that improvement in discoid lupus during atabrine was first reported by Prokoptchauk as early as 1940. Of 55 patients in Kierland's series, 17 had complete arrest of the disease and 15 had "more than 75 per cent" improvement. After stopping the drug, recurrences were frequent and during maintenance treatment (50 to 100 mg daily) several patients noted reactivation of skin lesions following exposure to sunlight

Goldman et al. (86) noted "great improvement" in discoid lupus in 14 of 21 patients given chloroquin diphosphate. The improvement occurred more slowly than with atabrine in some patients.

Severe side effects occurred in five of Kierland's (142) patients who had SLE, six weeks to six months after starting treatment although in three the skin had improved before the untoward effects appeared. The side effects included a "lichenoid" eruption in three, a pityriasis rosea-like eruption in one and in the fifth patient, fever, leucopenia, thrombocytopenia, and an increased sedimentation rate. These reactions cleared one to four months after discontinuing the drug. Fatal aplastic anemia following quinacrine therapy in chronic discoid LE has been reported (193).

(3) *Nitrogen mustards.* Following reports of beneficial effects of nitrogen mustards in various diseases of hypersensitivity, trials in SLE have been described

by several observers. Plaza de los Reyes noted beneficial effects in two patients (200). Rohn and Bond (219) treated five and were able to compare the effects of nitrogen mustard with ACTH in four One patient with pulmonary tuberculosis as well as SLE obtained remissions of 44, 217, and 21+ days, respectively, after each of three courses of nitrogen mustards, and the tuberculosis did not spread. In two patients, however, only brief remission of 17 and 20 days, respectively, took place and in the other two there was no response Of the two patients with the brief remissions, one had also a brief remission (14 days) on ACTH and the other a long period of improvement (210 days) Similarly, of the two patients with no response, one had no response to ACTH, but the other had two remissions of 300 and 205+ days, respectively

Dubois (58) gave nitrogen mustard and triethylene melamine (TEM) to 20 patients who were not responding to hormone therapy Of 11 with a nephrotic picture, nine were helped, but in two with non-edematous nephritis and seven without renal involvement no improvement occurred Two of the five given TEM developed agranulocytosis and one a fatal aplastic anemia. All were continued on cortisone or ACTH and in no case was a full remission induced

One of our patients (Case 26) received two courses of nitrogen mustards when she was erroneously thought to have a lymphoma It is difficult to interpret the course of events in this patient There were virtually no immediate beneficial effects but two periods of symptomatic relief ensued Over the two-year period the SLE progressed to involve both the joints and the kidneys

The use of nitrogen mustards in SLE does not appear to be therapeutically promising and is potentially hazardous

(4) *Vitamin B_{12}* The evidence that Vitamin B_{12} may benefit patients with SLE is meagre. Goldblatt (85) gave this substance to 17 patients with various forms of LE and reported improvement in all Only two had acute SLE at the time One patient became afebrile on the fourth treatment day and a 50 per cent decrease in the rash was observed after the third week The other had been on treatment for 52 weeks, had "80 per cent loss" of the dermatitis after five weeks, but did not become symptom-free until the 51st week

(5) *Para-aminobenzoic acid* Since light sensitization may occur both in patients with lupus erythematosus and in those given sulfonamides, and since para-aminobenzoic acid (PABA) is a metabolic antagonist to sulfonamides, Zarafonetis (274, 275) treated patients with various forms of lupus with PABA. Most of the patients (27 of 33) had disease largely confined to the skin and varying degrees of improvement occurred in the majority However, of the six classified as acute SLE four were unchanged, one had a "poor" response and one had a "good" response Furthermore, the author, who had administered this drug in a wide variety of disease states, indicated that reactions to PABA were more frequent in patients with lupus than in any other group One of our patients had a severe exacerbation of renal manifestations coincident with PABA administration Johnson and Meyer (131) observed subjective and objective improvement in four of five patients given PABA but in each instance this was not sustained No demonstrable change was seen in the fifth All subsequently

received cortisone and in each instance the response was more rapid than that following PABA.

XIII PROGNOSIS

a. Introduction

Data as to the duration of this disease in patients receiving no specific treatment are important as a background for the evaluation of therapy.

SLE may make its appearance with dramatic suddenness, or so insidiously that its presence is unsuspected for a long period. The frequency with which the disease develops obscurely, and the long interval of time elapsing before its recognition has lead to a false impression regarding its usual duration.

The dramatic events of the acute phases of the disease may detract attention from more subtle events that have gone before. For this reason, also, one must be cautious in depicting various phenomena such as idiopathic thrombocytopenia, epilepsy, and biological false positive tests for syphilis as commonly being the earliest manifestations of SLE. In many patients in our series in whom such events at first appeared to be the earliest evidence of the disease, careful analysis showed that other changes had been present antecedently, sometimes by many years.

The determination of survivorship figures in SLE presents several problems. The first of these is the definition of the cases included: the type of patients presenting themselves at a given institution, the diagnostic criteria, the chronicity of the disease, its variable pattern, and treatment. Secondly, there are different points of reference from which survivorship might be stated. Finally, there is the problem of coping with the variable length of follow-up for the patients coming under observation

The literature on prognosis in this disease is very limited and fails to deal satisfactorily with the problems of starting point and variable follow-up (104, 120, 129, 258) The most complete data on survivorship were presented by Jessar and his co-workers (129) on 103 patients, but the analysis of the observations may be misleading with regard to the handling of persons still alive who had been followed for variable times. In their final assessment the authors stated that "while the prognosis in SLE is unfavorable, it is likewise apparent that in some 20 per cent a duration of illness greater than five years may be expected" (p 728) Yet, on the same page they give a five-year death rate of 70 per cent, obtained by a different procedure. This inconsistency results from two di

known

tients

years from onset. Only four of these 26 were lost to observation and for the remaining 22 their fifth anniversary had not yet arrived. The 20 per cent survival figure was obtained by implicitly assuming that the four lost cases survived five years but that none of the 22 did. The 30 per cent survival rate was obtained by limiting the analysis to those cases that had an opportunity to be

followed five years. This result agrees with the results obtained by applying the analytical method used in this paper to all of Jessar's patients, taking due account of their length of follow-up. The estimate means that 12 of the 26 living cases will survive to their fifth anniversary.

There are serious difficulties in the interpretation of such survivorship figures as giving the natural history of the disease when the onset of the disease is chosen as the starting point. In the first place, as stated previously, the onset may be frequently vague in terms of both the assignment of the precise time of onset and the validity of the complaint as part of the disease. Moreover, since the cases were not seen at onset but at some later stage they must have been pre-dated and the survivorship figures are based in part on a backward look at the history of the case and in part on follow-up after diagnosis. The fallacy of considering such estimates as prognosis from onset may be clarified by an example. Consider an estimate of infant mortality from birth to one year obtained by selecting babies brought in for vaccination, pre-dating them to birth, and following them to their first birthday. Infant mortality estimated in this way will be erroneous because it fails to include all babies who have died during the first year of life before being presented for vaccination.

Similarly those patients with SLE surviving to and presenting themselves for diagnosis usually represent a biased group of those having an onset of the disease.

Another approach to prognosis has been to get the average duration of life from onset, by averaging the length of life of those who have died to the current date. Excluding the living cases and determining an average duration of life in those who have died almost always results in an under-estimate of life expectancy which may be substantial. Dubois and colleagues (59) quoted their own experience in these terms for the pre-treatment days, stating that they had no living patients in the pre-treatment series, but they compared their figures with those of other authors without the assurance that the latter also had no living patients. If this procedure were used in the cases included in our own analysis it would give a median duration of life *after diagnosis* of seven months whereas a correct analysis gives approximately four years.

One analysis dealing explicitly with all the observations, living and dead, and taking account of the variable lengths of follow-up, results in a "life table", which gives among other things the percentage surviving to various points of time from the selected starting point. If we take the diagnosis or some other point in the management of the case as the starting point from which cases are followed, no retrospective observations are involved, and we can arrive at prognosis from this point.

We are reporting here the results of such an analysis for patients diagnosed at the Johns Hopkins Hospital, prognosis being stated from date of diagnosis. These results are abstracted from a more extensive discussion dealing with the problems and methods of analysis of prognosis in long-time follow-up, scheduled to appear elsewhere (170).

tion of therapy. Therefore, no further breakdown, beyond the question of whether the patient received treatment or not, was performed.

On the basis of the history, an attempt was made to date the onset. When there was a question of validity of symptoms or signs we have selected the more definite and recent ones. The duration of time between the estimated onset of the disease and the date of diagnosis varied from less than a month to 25 years, but the distribution of these intervals is piled up toward the short intervals, as shown in Chart 5. One-fourth of the intervals are less than 1.1 years, one-half less than 2.6 years and three-fourths less than 6.8 years. The remaining fourth is scattered with diminishing frequency up to 25 years.

There is a slight tendency for the persons with shorter durations of disease at the time of diagnosis to be younger but this relationship is less pronounced than might have been anticipated. Of the cases with onset less than 2 years

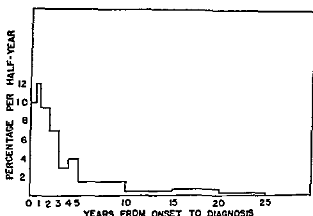


CHART 5. The interval from onset to diagnosis in 99 cases of SLE seen from 1949 through 1953

prior to diagnosis, 17 per cent were under age 20 compared with 5 per cent under this age for persons with longer durations prior to diagnosis. The median ages of the two distributions are almost identical, however, being 36.1 years and 36.8 years, respectively

c. *Prognosis From Time of Diagnosis*

The life table based on the total experience of the 99 cases yields the survivorship curve shown in Chart 6. The x-scale gives years measured from diagnosis, the origin being date of diagnosis; the ordinate is the percentage surviving to the various times. The deaths occur most rapidly within the first three months after diagnosis, 13 per cent of the cases dying within this time. Of patients diagnosed, 78 per cent survive to their first anniversary, 52 per cent to their fourth. The drop in this curve between any two points represents the percentage of the original group of diagnosed patients who die in the interval.

It is also of interest to consider the death rates during the different intervals

relative to the survivors at the beginning of the interval. The rapid death rate in the first three months is followed by a lower and virtually constant rate of 10 per cent per year. That is, of the survivors to any point, about 10 per cent will die in the following year.

The survivorship observed for this series of patients is very much more favorable than that cited from the literature. Jessar's series (loc. cit.) showed only 38 per cent surviving four years after *onset*, whereas our series had 50 per cent surviving four years after *diagnosis*. This difference in percentages is in the opposite direction from that which would be expected to result from the difference in the selected starting points and, therefore, the discrepancy between the two is greater than that between the percentages quoted. Jessar's series was composed of 44 of their own patients observed during the 15 years prior to 1952 and 59, among the 279 gathered from the literature in the years 1948–1952, in whom

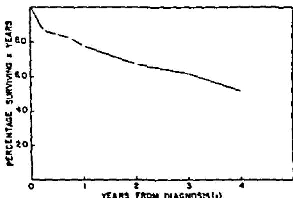


CHART 6 Survivorship after diagnosis in 99 cases of SLE seen from 1949 through 1953

there was sufficient information to estimate duration of illness from onset. The more favorable survivorship in our patients when compared with Jessar's series may be the result of several factors: 1) the possibility that on the average our patients were less severely ill than theirs. This might be due to the inclusion in our series of milder, or earlier, cases, discovered either by the L.E. cell test or by the earlier recognition of this disease by physicians in general, so that earlier diagnoses are made. 2) This may result from beneficial effects of hormone therapy. Roughly three-fourths (75 of 99) of our patients received such therapy, in one form or another, whereas theirs received none. 3) This may be a consequence of one or more of the several factors which make one hospital's cases unlike another's.

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diagnosis was made on clinical grounds (and confirmed by the L.E. cell test) and those in whom the diagnosis was in varying degrees suspected clinically, but established by the demonstration of these cells.

It is, thus, tempting to entertain the possibility that the effects of hormone treatment, begun in mid-1949, were largely responsible for the enhanced survivorship in our patients when compared with that of Jessar's series. However, such a conclusion would not be sound because of the limited experience to date, and absence of an acceptable group of untreated patients in the years 1949 through 1953 to serve as a control. Haserick (104) attempted a comparison of hormone-treated with non-hormone-treated patients, the diagnosis in all being confirmed by the presence of L.E. cells, and assigned to the treatment of lengthening of life. However, of his 83 patients only ten were in the untreated series and these antedated the treated cases, thus not constituting a concurrent untreated control. The data from his study would seem to be, therefore, insufficient to allow any firm conclusions to be drawn. In order to assess with accuracy the value of any specific therapy in this disease, it is essential to carry out a planned study having some sort of random assignment of patients to different treatment

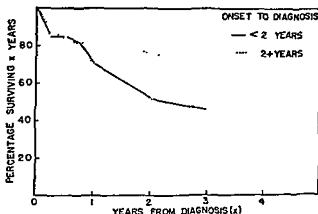


CHART 7. Survivorship after diagnosis, by interval from onset to diagnosis, in 99 cases of SLE seen from 1949 through 1953

schedules. With the evidence suggesting that hormone therapy may be ad- [illegible] effect on prognosis, [illegible] time from onset to diagnosis The numbers were too small to permit detailed break-downs into sub-groups and age was considered in the two broad groups; under and over age 40. No significant difference was found in the two survivorship curves.

With regard to interval between onset and diagnosis, the patients were again divided into two groups, under and over two years. Forty-one patients were diagnosed less than two years after onset of symptoms, and 58 patients two or more years after onset. The numbers are so small that the life tables are not carried beyond the third anniversary and even over this interval the standard errors are large Nevertheless, there is a significant difference in survivorship at the second and third anniversaries (at the 5 per cent level of significance), in

favor of the cases with longer intervals. Chart 7 shows that within the first year after diagnosis the survivorship curves are identical, but after the first year the cases with more recent onset, die off more rapidly. The actual size of the difference is substantial at the 3rd anniversary, 72 per cent compared with 46 per cent but as noted above these percentages have a large sampling variation and the size of the difference is not well established.

The interpretation of this difference seems most likely to be in the selection of the cases, since it is unlikely that early diagnosis per se should be a disadvantage. The type of case that presents serious enough symptoms early in its course to bring the patient to the attention of the doctor and enable him to make a diagnosis, may well be the type that progresses more rapidly thereafter.

XIV SUMMARY

Increasing familiarity with the varied clinical manifestations of SLE, together with improved methods of definitive diagnosis, have led to an altered concept of the character of this disease It has become apparent that the course is frequently chronic, associated with exacerbations and remissions over a period of many years The disease is often characterized by recurrent mild illnesses, seemingly unrelated, with prolonged asymptomatic intervals Even when severe manifestations appear, they may be followed by spontaneous improvement or complete remissions. In some patients, serologic abnormalities antedate by years other evidences of SLE, indicating that the disease may remain clinically inactive for indefinite periods of time after the onset

Our present knowledge is based largely on retrospective study of cases of full blown SLE, for only recently has it been possible to recognize the disease in its mild or early forms. It is well known that fulminating or fatal illness may occur abruptly or after many years of mild symptoms However, it remains to be determined whether all cases must necessarily terminate in this fashion. Prolonged observations will be required to establish the course of the disease in the mild cases now being recognized. It is entirely possible that some patients may recover, or that the disease will fail to progress The possibility cannot be overlooked that even now we are failing to recognize many mild cases of SLE because of the lack of an adequate diagnostic test It should be emphasized that the negative L E. cell test does not exclude the existence of this disease.

The cause of SLE remains obscure, but two features have attracted special attention. One is the almost constant presence of abnormalities of the serum proteins, and the other is the evidence of disease of collagen. The manner in which these phenomena are interrelated and the mechanism of their production have not been elucidated While manifestations of hypersensitivity are common in patients with SLE, it has not been established that hypersensitive reactions are of etiologic significance

Definitive treatment will have to await a better understanding of the pathogenesis of SLE. Striking suppression of many of the signs and symptoms of the disease may be obtained with hormone therapy, but others are unaffected, and complications occur frequently. Whether or not life is prolonged by such therapy

It is, thus, tempting to entertain the possibility that the effects of hormone treatment, begun in mid-1949, were largely responsible for the enhanced survivorship in our patients when compared with that of Jessar's series. However, such a conclusion would not be sound because of the limited experience to date, and absence of an acceptable group of untreated patients in the years 1949 through 1953 to serve as a control. Haserick (104) attempted a comparison of hormone-treated with non-hormone-treated patients, the diagnosis in all being confirmed by the presence of L.E. cells, and assigned to the treatment of lengthening of life. However, of his 83 patients only ten were in the untreated series and these antedated the treated cases, thus not constituting a concurrent untreated control. The data from his study would seem to be, therefore, insufficient to allow any firm conclusions to be drawn. In order to assess with accuracy the value of any specific therapy in this disease, it is essential to carry out a planned study having some sort of random assignment of patients to different treatment

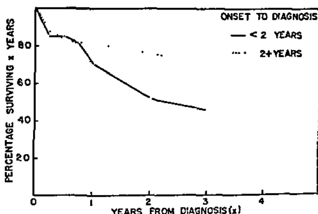


CHART 7. Survivorship after diagnosis, by interval from onset to diagnosis, in 99 cases of SLE seen from 1949 through 1953

schedules With the evidence suggesting that hormone therapy may be advantageous in SLE, this would be exceedingly difficult to do.

Two specific factors were studied in our cases as to their effect on prognosis, namely: age at the time of diagnosis, and the duration of time from onset to diagnosis The numbers were too small to permit detailed break-downs into sub-groups and age was considered in the two broad groups; under and over age 40. No significant difference was found in the two survivorship curves.

With regard to interval between onset and diagnosis, the patients were again divided into two groups, under and over two years. Forty-one patients were [illegible] patients two or [illegible] not [illegible] dard [illegible] errors are large. Nevertheless, there is a significant difference in [illegible] at the second and third anniversaries (at the 5 per cent level of significance), in

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cannot at this time be accurately ascertained, but the evidence to date is in the affirmative.

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